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Founded in 1925

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ReoPro®
abciximab

America

Hope for a better life

ReoPro® (abciximab)

Confidence for better outcomes

- ReoPro has been shown to reduce ischemic events,[1]* infarct size,[2] and 1-year mortality[3] after PCI with stent[3]
- ReoPro improves both epicardial[4] and microvascular flow[5]

* D/MI/UTVR at 30 days.
† Data from earlier studies with balloon angioplasty were not suggestive of this mortality benefit.

Important Safety Information

Indication

ReoPro is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications:

- In patients undergoing percutaneous coronary intervention
- In patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours

Safety and efficacy of ReoPro use in patients not undergoing percutaneous coronary intervention have not been established.

ReoPro is intended for use with aspirin and heparin and has been studied only in that setting.

Bleeding risk. ReoPro has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation agents, e.g., from heparin or other anticoagulants. The risk of a major bleed due to ReoPro therapy is increased in patients receiving thrombolytics and should be weighed against the anticipated benefits.

Guidelines for reduction in bleeding. Use of a low-dose, weight-adjusted heparin regimen, discontinuation of heparin on completion of the procedure with removal of the arterial sheath within 6 hours, careful vascular access site management and careful patient management, including attention to other potential bleeding sites, use of a weight-adjusted bolus and continuous infusion dose of ReoPro.

Thrombocytopenia. In clinical trials, patients treated with ReoPro were more likely than patients who received placebo to experience decreases in platelet counts, including severe thrombocytopenia (also see Readministration).

Readministration of ReoPro. Administration of ReoPro may result in the formation of human anti-chimeric antibodies (HACA) that could potentially cause allergic or hypersensitivity reactions (including anaphylaxis), thrombocytopenia, or diminished benefit upon readministration. In a registry study of ReoPro readministration (1342 treatments in 1286 patients), there were no reports of serious allergic reactions or anaphylaxis. Thrombocytopenia was observed at higher rates in the readministration study than in the Phase 3 studies of first-time administration, suggesting that readministration may be associated with an increased incidence and severity of thrombocytopenia. This increased risk was associated with a history of thrombocytopenia on prior ReoPro exposure, a positive HACA assay at baseline, and readministration within 30 days.

Allergic reactions (including anaphylaxis). Allergic reactions, some of which were anaphylaxis (sometimes fatal), have been reported rarely in patients treated with ReoPro. Patients with allergic reactions should receive appropriate treatment. Treatment of anaphylaxis should include immediate discontinuation of ReoPro administration and initiation of resuscitative measures.

Contraindications. Because ReoPro may increase the risk of bleeding, use is contraindicated in the following clinical situations: active internal bleeding; recent (within 6 weeks) gastrointestinal or genitourinary bleeding of clinical significance; history of cerebrovascular accident (CVA) within 2 years, or CVA with a significant residual neurological deficit; bleeding diathesis; administration of oral anticoagulants within 7 days unless prothrombin time ≤1.2 times control; thrombocytopenia (<100,000 cells/μL); recent (within 6 weeks) major surgery or trauma; intracranial neoplasm, arteriovenous malformation, or aneurysm; severe uncontrolled hypertension; presumed or documented history of vasculitis; use of intravenous dextran before percutaneous coronary intervention, or intent to use it during intervention; known hypersensitivity to any component of this product or to murine proteins.

See reverse page for Brief Summary.

centocor B.V.

Lilly

ReoPro®
abciximab

For intravenous administration

BRIEF SUMMARY. Consult the Prescribing Information for full prescribing information.

INDICATIONS AND USAGE: Abciximab is indicated as an adjunct to percutaneous coronary intervention for the prevention of cardiac ischemic complications

- in patients undergoing percutaneous coronary intervention
- in patients with unstable angina not responding to conventional medical therapy when percutaneous coronary intervention is planned within 24 hours

Safety and efficacy of Abciximab use in patients not undergoing percutaneous coronary intervention have not been established.

Abciximab is intended for use with aspirin and heparin and has been studied only in that setting, as described in CLINICAL STUDIES.

CONTRAINDICATIONS: Because Abciximab may increase the risk of bleeding, Abciximab is contraindicated in the following clinical situations:

- Active internal bleeding
- Recent (within six weeks) gastrointestinal (GI) or genitourinary (GU) bleeding of clinical significance
- History of cerebrovascular accident (CVA) within two years, or CVA with a significant residual neurological deficit
- Bleeding diathesis
- Administration of oral anticoagulants within seven days unless prothrombin time is ≤ 1.2 times control
- Thrombocytopenia (< 100,000 cells/μL)
- Recent (within six weeks) major surgery or trauma
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Severe uncontrolled hypertension
- Presumed or documented history of vasculitis
- Use of intravenous dextran before PCI, or intent to use it during an intervention

Abciximab is also contraindicated in patients with known hypersensitivity to any component of this product or to murine proteins.

WARNINGS: Bleeding Events—Abciximab has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation, e.g., from heparin, other anticoagulants, or thrombolytics (see ADVERSE REACTIONS: Bleeding).

The risk of major bleeds due to Abciximab therapy is increased in patients receiving thrombolytics and should be weighed against the anticipated benefits.

Should serious bleeding occur that is not controllable with pressure, the infusion of Abciximab and any concomitant heparin should be stopped.

Allergic Reactions (including anaphylaxis)—Allergic reactions, some of which were anaphylaxis (sometimes fatal), have been reported rarely in patients treated with ReoPro. Patients with allergic reactions should receive appropriate treatment. Treatment of anaphylaxis should include immediate discontinuation of ReoPro administration and initiation of resuscitative measures.

PRECAUTIONS: Bleeding Precautions—To minimize the risk of bleeding with Abciximab, it is important to use a low-dose, weight-adjusted heparin regimen, a weight-adjusted Abciximab bolus and infusion, strict anticoagulation guidelines, careful vascular access site management, discontinuation of heparin after the procedure and early femoral arterial sheath removal.

Therapy with Abciximab requires careful attention to all potential bleeding sites including catheter insertion sites, arterial and venous puncture sites, cutdown sites, needle puncture sites, and gastrointestinal, genitourinary, pulmonary (alveolar), and retroperitoneal sites.

Arterial and venous punctures, intramuscular injections, and use of urinary catheters, nasotracheal intubation, nasogastric tubes and automatic blood pressure cuffs should be minimized. When obtaining intravenous access, non-compressible sites (e.g., subclavian or jugular veins) should be avoided. Saline or heparin locks should be considered for blood drawing. Vascular puncture sites should be documented and monitored. Gentle care should be provided when removing dressings.

Femoral artery access site—Arterial access site care is important to prevent bleeding. Care should be taken when attempting vascular access that only the anterior wall of the femoral artery is punctured, avoiding a Seldinger (through and through) technique for obtaining sheath access. Femoral vein sheath placement should be avoided unless needed. While the vascular sheath is in place, patients should be maintained on complete bed rest with the head of the bed ≤ 30° and the affected limb restrained in a straight position. Patients may be medicated for back/groin pain as necessary.

Discontinuation of heparin immediately upon completion of the procedure and removal of the arterial sheath within six hours is strongly recommended if APTT ≤ 50 sec or ACT ≤ 175 sec (See PRECAUTIONS: Laboratory Tests). In all circumstances, heparin should be discontinued at least two hours prior to arterial sheath removal.

Following sheath removal, pressure should be applied to the femoral artery for at least 30 minutes using either manual compression or a mechanical device for hemostasis. A pressure dressing should be applied following hemostasis. The patient should be maintained on bed rest for six to eight hours following sheath removal or discontinuation of Abciximab, or four hours following discontinuation of heparin, whichever is later. The pressure dressing should be removed prior to ambulation. The sheath insertion site and distal pulses of affected leg(s) should be frequently checked while the femoral artery sheath is in place and for six hours after femoral artery sheath removal. Any hematoma should be measured and monitored for enlargement.

The following conditions have been associated with an increased risk of bleeding and may be additive with the effect of Abciximab in the angioplasty setting. PCI within 12 hours of the onset of symptoms for acute myocardial infarction, prolonged PCI (lasting more than 70 minutes) and failed PCI.

Use of Thrombolytics, Anticoagulants and Other Antiplatelet Agents—In the EPIC, EPILOG, CAPTURE, and EPISTENT trials, Abciximab was used concomitantly with heparin and aspirin. For details of the anticoagulation algorithms used in these clinical trials, see CLINICAL STUDIES: Anticoagulation. Because Abciximab inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory drugs, dipyridamole, and ticlopidine.

In the EPIC trial, there was limited experience with the administration of Abciximab with low molecular weight dextran. Low molecular weight dextran was usually given for the deployment of a coronary stent, for which oral anticoagulants were also given. In the 11 patients who received low molecular weight dextran with Abciximab, five had major bleeding events and four had minor bleeding events. None of the five placebo patients treated with low molecular weight dextran had a major or minor bleeding event (see CONTRAINDICATIONS).

Because of observed synergistic effects on bleeding, Abciximab therapy should be used judiciously in patients who have received systemic thrombolytic therapy. The GUSTO V trial randomized patients with acute myocardial infarction to treatment with combined Abciximab and half-dose Reteplase, or full-dose Reteplase alone (15). In this trial, the incidence of moderate or severe nonintracranial bleeding was increased in those patients receiving Abciximab and half-dose Reteplase versus those receiving Reteplase alone (4.6% versus 2.3%, respectively).

Thrombocytopenia—Thrombocytopenia, including severe thrombocytopenia, has been observed with Abciximab administration (See Adverse Reactions: Thrombocytopenia). Platelet counts should be monitored prior to, during, and after treatment with Abciximab. Acute decreases in platelet count should be differentiated between true thrombocytopenia and pseudothrombocytopenia (See Precautions: Laboratory Tests). If true thrombocytopenia is verified, Abciximab should be immediately discontinued and the condition appropriately monitored and treated.

In clinical trials, patients who developed thrombocytopenia were followed with daily platelet counts until their platelet count returned to normal. Heparin and aspirin were discontinued for platelet counts below 60,000 cells/μL and platelets were transfused for a platelet count below 50,000 cells/μL. Most cases of severe thrombocytopenia (< 50,000 cells/μL) occurred within the first 24 hours of Abciximab administration.

In a registry study of Abciximab readministration, a history of thrombocytopenia associated with prior use of Abciximab was predictive of an increased risk of recurrent thrombocytopenia (See Adverse Reactions: Thrombocytopenia). Readministration within 30 days was associated with an increased incidence and severity of thrombocytopenia, as was a positive human anti-chimeric antibody (HACA) test at baseline, compared to the rates seen in studies with first administration.

Restoration of Platelet Function—In the event of serious uncontrolled bleeding or the need for emergency surgery, Abciximab should be discontinued. If platelet function does not return to normal, it may be restored, at least in part, with platelet transfusions.

Laboratory Tests—Before infusion of Abciximab, prothrombin time, ACT, APTT, and platelet count should be measured to identify pre-existing hemostatic abnormalities.

Based on an integrated analysis of data from all studies, the following guidelines may be utilized to minimize the risk for bleeding:

- When Abciximab is initiated 18 to 24 hours before PCI, the APTT should be maintained between 60 and 85 seconds during the Abciximab and heparin infusion period.
- During PCI the ACT should be maintained between 200 and 300 seconds.
- If anticoagulation is continued in these patients following PCI, the APTT should be maintained between 55 and 75 seconds.

The APTT or ACT should be checked prior to arterial sheath removal. The sheath should not be removed unless APTT ≤ 50 seconds or ACT ≤ 175 seconds.

Platelet counts should be monitored prior to treatment, two to four hours following the bolus dose of Abciximab and at 24 hours or prior to discharge, whichever is first. If a patient experiences an acute platelet decrease (e.g., a platelet decrease to less than 100,000 cells/μL and a decrease of at least 25% from pre-treatment value), additional platelet counts should be determined. Platelet monitoring should continue until platelet counts return to normal.

To exclude pseudothrombocytopenia, a laboratory artifact due to *in vitro* anticoagulant interaction, blood samples should be drawn in three separate tubes containing ethylenediaminetetraacetic acid (EDTA), citrate and heparin, respectively. A low platelet count in EDTA but not in heparin and/or citrate is supportive of a diagnosis of pseudothrombocytopenia.

Readministration—Administration of Abciximab may result in the formation of HACA that could potentially cause allergic or hypersensitivity reactions (including anaphylaxis), thrombocytopenia or diminished benefit upon readministration of Abciximab (See Adverse Reactions: Immunogenicity).

Readministration of Abciximab to patients undergoing PCI was assessed in a registry that included 1342 treatments in 1286 patients. Most patients were receiving their second Abciximab exposure; 15% were receiving the third or subsequent exposure. The overall rate of HACA positivity prior to the readministration was 6% and increased to 27% post-readministration. There were no reports of serious allergic reactions or anaphylaxis. Thrombocytopenia was observed at higher rates in the readministration study than in the phase 3 studies of first-time administration (See Precautions: Thrombocytopenia and Adverse Reactions: Thrombocytopenia), suggesting that readministration may be associated with an increased incidence and severity of thrombocytopenia.

Drug Interactions—Formal drug interaction studies with Abciximab have not been conducted. Abciximab has been administered to patients with ischemic heart disease treated concomitantly with a broad range of medications used in the treatment of angina, myocardial infarction and hypertension. These medications have included heparin, warfarin, beta-adrenergic receptor blockers, calcium channel antagonists, angiotensin converting enzyme inhibitors, intravenous and oral nitrates, ticlopidine, and aspirin. Heparin, other anticoagulants, thrombolytics, and antiplatelet agents are associated with an increase in bleeding. Patients with HACA titers may have allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

Carcinogenesis, Mutagenesis and Impairment of Fertility—*In vitro* and *in vivo* mutagenicity studies have not demonstrated any mutagenic effect. Long-term studies in animals have not been performed to evaluate the carcinogenic potential or effects on fertility in male or female animals.

Pregnancy Category C—Animal reproduction studies have not been conducted with Abciximab. It is also not known whether Abciximab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Abciximab should be given to a pregnant woman only if clearly needed.

Nursing Mothers—It is not known whether this drug is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Abciximab is administered to a nursing woman.

Pediatric Use—Safety and effectiveness in pediatric patients have not been studied.

Geriatric Use—Of the total number of 7860 patients in the four Phase 3 trials, 2933 (37%) were 65 and over, while 653 (8%) were 75 and over. No overall differences in safety or efficacy were observed between patients of age 65 to less than 75 as compared to younger patients. The clinical experience is not adequate to determine whether patients of age 75 or greater respond differently than younger patients.

ADVERSE REACTIONS: Bleeding—Abciximab has the potential to increase the risk of bleeding, particularly in the presence of anticoagulation, e.g., from heparin, other anticoagulants or thrombolytics. Bleeding in the Phase 3 trials was classified as major, minor or insignificant by the criteria of the Thrombolysis in Myocardial Infarction study group (16). Major bleeding events were defined as either an intracranial hemorrhage or a decrease in hemoglobin greater than 5 g/dL. Minor bleeding events included spontaneous gross hematuria, spontaneous hematemesis, observed blood loss with a hemoglobin decrease of more than 3 g/dL, or a decrease in hemoglobin of at least 4 g/dL without an identified bleeding site. Insignificant bleeding events were defined as a decrease in hemoglobin of less than 3 g/dL or a decrease in hemoglobin between 3-4 g/dL without observed bleeding. In patients who received transfusions, the number of units of blood lost was estimated through an adaptation of the method of Landefeld, et al. (17).

In the EPIC trial, in which a non-weight-adjusted, longer-duration heparin dose regimen was used, the most common complication during Abciximab therapy was bleeding during the first 36 hours. The incidences of major bleeding, minor bleeding and transfusion of blood products were significantly increased. Major bleeding occurred in 10.6% of patients in the Abciximab bolus plus infusion arm compared with 3.3% of patients in the placebo arm. Minor bleeding was seen in 16.8% of Abciximab bolus plus infusion patients and 9.2% of placebo patients (7). Approximately 70% of Abciximab-treated patients with major bleeding had bleeding at the arterial access site in the groin. Abciximab-treated patients also had a higher incidence of major bleeding events from gastrointestinal, genitourinary, retroperitoneal, and other sites.

Bleeding rates were reduced in the CAPTURE trial, and further reduced in the EPILOG and EPISTENT trials by use of modified dosing regimens and specific patient management techniques. In EPILOG and EPISTENT, using the heparin and Abciximab dosing, sheath removal and arterial access site guidelines described under PRECAUTIONS, the incidence of major bleeding in patients treated with Abciximab and low-dose, weight-adjusted heparin was not significantly different from that in patients receiving placebo.

Subgroup analyses in the EPIC and CAPTURE trials showed that non-CABG major bleeding was more common in Abciximab patients weighing ≤ 75 kg. In the EPILOG and EPISTENT trials, which used weight-adjusted heparin dosing, the non-CABG major bleeding rates for Abciximab-treated patients did not differ substantially by weight subgroup.

Although data are limited, Abciximab treatment was not associated with excess major bleeding in patients who underwent CABG surgery. (The range among all treatment arms was 3-5% in EPIC, and 1-2% in the CAPTURE, EPILOG, and EPISTENT trials.) Some patients with prolonged bleeding times received platelet transfusions to correct the bleeding time prior to surgery. (See PRECAUTIONS: Restoration of Platelet Function.)

The rates of major bleeding, minor bleeding and bleeding events requiring transfusions in the CAPTURE, EPILOG, and EPISTENT trials are shown in Table 1. The rates of insignificant bleeding events are not included in Table 1.

Pulmonary alveolar hemorrhage has been rarely reported during use of Abciximab. This can present with any or all of the following in close association with ReoPro administration: hypoxemia, diffuse infiltrates on chest x-ray, hemoptysis, or an unexplained drop in hemoglobin.

Table 1
NON-CABG BLEEDING IN TRIALS OF PERCUTANEOUS CORONARY INTERVENTION (EPILOG, EPISTENT and CAPTURE)

	Number of Patients with Bleeds (%)		
EPILOG and EPISTENT:	Placebo[1] (n=1748)	Abciximab + Low-dose Heparin[2] (n=2525)	Abciximab + Standard-dose Heparin[3] (n=918)
Major[4]	18 (1.0)	21 (0.8)	17 (1.9)
Minor[5]	46 (2.6)	82 (3.2)	70 (7.6)
Requiring transfusion[6]	15 (0.9)	13 (0.5)	7 (0.8)
CAPTURE:	Placebo[1] (n=635)		Abciximab[7] (n=630)
Major[4]	12 (1.9)		24 (3.8)
Minor[5]	13 (2.0)		30 (4.8)
Requiring transfusion[6]	9 (1.4)		15 (2.4)

[1] Patients who had bleeding in more than one classification are counted only once according to the most severe classification. Patients with multiple bleeding events of the same classification are also counted once within that classification.
[2] Patients with major non-CABG bleeding who received packed red blood cells or whole blood transfusion.
[3] Standard-dose heparin with or without stent (EPILOG and EPISTENT)
[4] Low-dose heparin with or without stent (EPILOG and EPISTENT)
[5] Standard-dose heparin (EPILOG)
[6] Standard-dose heparin (CAPTURE)

Intracranial Hemorrhage and Stroke—The total incidence of intracranial hemorrhage and non-hemorrhagic stroke across all four trials was not significantly different, 9/3023 for placebo patients and 15/4680 for Abciximab-treated patients. The incidence of intracranial hemorrhage was 3/3023 for placebo patients and 7/4680 for Abciximab patients.

Thrombocytopenia—In the clinical trials, patients treated with Abciximab were more likely than patients treated with placebo to experience decreases in platelet counts.

Among patients in the EPILOG and EPISTENT trials who were treated with Abciximab plus low-dose heparin, the proportion of patients with any thrombocytopenia (platelets less than 100,000 cells/μL) ranged from 2.5 to 3.0%. The incidence of severe thrombocytopenia (platelets less than 50,000 cells/μL) ranged from 0.4 to 1.0% and platelet transfusions were required in 0.9 to 1.1%, respectively. Modestly lower rates were observed among patients treated with placebo plus standard-dose heparin. Overall higher rates were observed among patients in the EPIC and CAPTURE trials treated with Abciximab plus longer duration heparin: 2.6 to 5.2% were found to have any thrombocytopenia, 0.9 to 1.7% had severe thrombocytopenia, and 2.1 to 5.5% required platelet transfusion, respectively.

In a readministration registry study of patients receiving a second or subsequent exposure to Abciximab (See Precautions: Readministration) the incidence of any degree of thrombocytopenia was 5%, with an incidence of profound thrombocytopenia of 2% (<20,000 cell/μL). Factors associated with an increased risk of thrombocytopenia were a history of thrombocytopenia on previous Abciximab exposure, readministration within 30 days, and a positive HACA assay prior to the readministration.

Among 14 patients who had thrombocytopenia associated with a prior exposure to Abciximab, 7 (50%) had recurrent thrombocytopenia. In 130 patients with a readministration interval of 30 days or less, 25 (19%) developed thrombocytopenia. Severe thrombocytopenia occurred in 19 of these patients. Among the 71 patients who had a positive HACA assay at baseline, 11 (15%) developed thrombocytopenia, 7 of which were severe.

Other Adverse Reactions—Table 2 shows adverse events other than bleeding and thrombocytopenia from the combined EPIC, EPILOG and CAPTURE trials which occurred in patients in the bolus plus infusion arm at an incidence of more than 0.5% higher than in those treated with placebo.

Table 2
ADVERSE EVENTS AMONG TREATED PATIENTS IN THE EPIC, EPILOG, AND CAPTURE TRIALS

Event	Placebo (n=2226)	Bolus + Infusion (n=3111)
	Number of Patients (%)	
Cardiovascular system		
Hypotension	230 (10.3)	447 (14.4)
Bradycardia	79 (3.5)	140 (4.5)
Gastrointestinal system		
Nausea	255 (11.5)	423 (13.6)
Vomiting	152 (6.8)	226 (7.3)
Abdominal pain	48 (2.2)	97 (3.1)
Miscellaneous		
Back pain	304 (13.7)	546 (17.6)
Chest pain	208 (9.3)	356 (11.4)
Headache	122 (5.5)	209 (6.7)
Puncture site pain	58 (2.6)	113 (3.6)
Peripheral edema	25 (1.1)	49 (1.6)

The following additional adverse events from the EPIC, EPILOG and CAPTURE trials were reported by investigators for patients treated with a bolus plus infusion of Abciximab at incidences which were less than 0.5% higher than for patients in the placebo arm.

Cardiovascular System: ventricular tachycardia (1.4%), pseudoaneurysm (0.8%), palpitation (0.5%), arteriovenous fistula (0.4%), incomplete AV block (0.3%), nodal arrhythmia (0.2%), complete AV block (0.1%), embolism (limb)(0.1%); thrombophlebitis (0.1%);

Gastrointestinal System: dyspepsia (2.1%), diarrhea (1.1%), ileus (0.1%), gastroesophageal reflux (0.1%);

Hemic and Lymphatic System: anemia (1.3%), leukocytosis (0.5%), petechiae (0.2%);

Nervous System: dizziness (2.9%), anxiety (1.7%), abnormal thinking (1.3%), agitation (0.7%), hypesthesia (0.6%), confusion (0.5%), muscle contractions (0.4%), coma (0.2%), hypertonia (0.2%), diplopia (0.1%);

Respiratory System: pneumonia (0.4%), rales (0.4%), pleural effusion (0.3%), bronchitis (0.3%), bronchospasm (0.3%), pleurisy (0.2%), pulmonary embolism (0.2%), rhonchi (0.1%);

Musculoskeletal System: myalgia (0.2%);

Urogental System: urinary retention (0.7%), dysuria (0.4%), abnormal renal function (0.4%), frequent micturition (0.1%), cystalgia (0.1%), urinary incontinence (0.1%), prostatitis (0.1%);

Miscellaneous: pain (5.4%), sweating increased (1.0%), asthenia (0.7%), incisional pain (0.6%), pruritus (0.5%), abnormal vision (0.3%), edema (0.3%), wound (0.2%), abscess (0.2%), cellulitis (0.2%), peripheral coldness (0.2%), injection site pain (0.1%), dry mouth (0.1%), pallor (0.1%), diabetes mellitus (0.1%), hyperkalemia (0.1%), enlarged abdomen (0.1%), bullous eruption (0.1%), inflammation (0.1%), drug toxicity (0.1%).

Immunogenicity—As with all therapeutic proteins, there is a potential for immunogenicity. In the EPIC, EPILOG, and CAPTURE trials, positive HACA responses occurred in approximately 5.8% of these patients receiving a first exposure to Abciximab. No increase in hypersensitivity or allergic reactions was observed with Abciximab treatment.

In a study of readministration of Abciximab to patients (See Precautions: Readministration) the overall rate of HACA positivity prior to the readministration was 6% and increased post-readministration to 27%. Among the 36 subjects receiving a fourth or greater Abciximab exposure, HACA positive assays were observed post-readministration in 16 subjects (44%). There were no reports of serious allergic reactions or anaphylaxis. HACA positive status was associated with an increased risk of thrombocytopenia (See Precautions: Thrombocytopenia).

The data reflect the percentage of patients whose test results were considered positive for antibodies to Abciximab using an ELISA assay, and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Abciximab with the incidence of antibodies to other products may be misleading.

OVERDOSAGE: There has been no experience of overdosage in human clinical trials.

Revision Date: November 16, 2005

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Lilly Distributed by: Eli Lilly and Company Indianapolis, IN 46285

ReoPro® (Abciximab)

ReoPro® (Abciximab)

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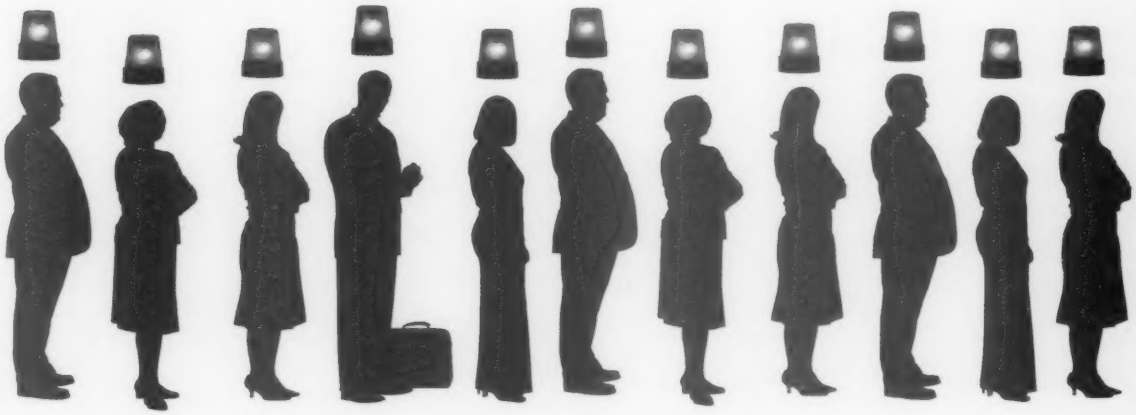
Patient, after patient, after patient...



More than 2 million MPI procedures using Adenoscan were performed last year in patients with suspected coronary artery disease.[1] For your patients unable to exercise adequately, Adenoscan can provide important risk stratification information to aid in clinical decision-making.[2-4]

Remember Adenoscan, the most widely used pharmacologic stress agent.[1]

May be managed conservatively

May benefit from aggressive management

IMPORTANT SAFETY INFORMATION

Intravenous Adenoscan® (adenosine injection) is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately.

Approximately 2.6% and 0.8% of patients developed second- and third-degree AV block, respectively. All episodes of AV block have been asymptomatic, transient, and did not require intervention; less than 1% required termination of adenosine infusion.

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk.

Side effects that were seen most often included flushing (44%), chest discomfort (40%), and dyspnea (28%). Side effects usually resolve quickly when infusion is terminated and generally do not interfere with test results.

Despite adenosine's short half-life, 10.6% of the side effects started several hours after the infusion terminated, and 8.4% of the side effects that began during the infusion persisted for up to 24 hours after infusion. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

Please see brief summary of prescribing information on adjacent page.

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Adenoscan helps you see.

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ADENOSCAN®
adenosine injection

BRIEF SUMMARY

ADENOSCAN®
adenosine injection

For Intravenous Infusion Only

DESCRIPTION

Adenosine is an endogenous nucleoside occurring in all cells of the body. It is chemically 6-amino-9-beta-D-ribofuranosyl-9 H-purine.

Adenosine is a white crystalline powder. It is soluble in water and practically insoluble in alcohol. Solubility increases by warming and lowering the pH of the solution.

Each Adenoscan vial contains a sterile, non-pyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in Water for Injection, q.s. The pH of the solution is between 4.5 and 7.5.

INDICATIONS AND USAGE:

Intravenous Adenoscan is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately.

(See **WARNINGS**).

CONTRAINDICATIONS:

Intravenous Adenoscan should not be administered to individuals with:

1. Second- or third-degree AV block (except in patients with a functioning artificial pacemaker).
2. Sinus node disease, such as sick sinus syndrome or symptomatic bradycardia (except in patients with a functioning artificial pacemaker).
3. Known or suspected bronchoconstrictive or bronchospastic lung disease (e.g., asthma).
4. Known hypersensitivity to adenosine.

WARNINGS:

Fatal Cardiac Arrest, Life Threatening Ventricular Arrhythmias, and Myocardial Infarction

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and nonfatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk. Appropriate resuscitative measures should be available.

Sinoatrial and Atrioventricular Nodal Block

Adenoscan exerts a direct depressant effect on the SA and AV nodes and has the potential to cause first-, second- or third-degree AV block, or sinus bradycardia. Approximately 6.3% of patients develop AV block with Adenoscan, including first-degree (2.9%), second-degree (2.6%) and third-degree (0.8%) heart block. All episodes of AV block have been asymptomatic, transient, and did not require intervention. Adenoscan can cause sinus bradycardia. Adenoscan should be used with caution in patients with pre-existing first-degree AV block or bundle branch block and should be avoided in patients with high-grade AV block or sinus node dysfunction (except in patients with a functioning artificial pacemaker). Adenoscan should be discontinued in any patient who develops persistent or symptomatic high-grade AV block. Sinus pause has been rarely observed with adenosine infusions.

Hypotension

Adenoscan is a potent peripheral vasodilator and can cause significant hypotension. Patients with an intact baroreceptor reflux mechanism are able to maintain blood pressure and tissue perfusion in response to Adenoscan by increasing heart rate and cardiac output. However, Adenoscan should be used with caution in patients with autonomic dysfunction, stenotic valvular heart disease, pericarditis or pericardial effusions, stenotic carotid artery disease with cerebrovascular insufficiency, or uncorrected hypovolemia, due to the risk of hypotensive complications in these patients. Adenoscan should be discontinued in any patient who develops persistent or symptomatic hypotension.

Hypertension

Increases in systolic and diastolic pressure have been observed (as great as 140 mm Hg systolic in one case) concomitant with Adenoscan infusion; most increases resolved spontaneously within several minutes, but in some cases, hypertension lasted for several hours.

Bronchoconstriction

Adenoscan is a respiratory stimulant (probably through activation of carotid body chemoreceptors) and intravenous administration in man has been shown to increase minute ventilation (Ve) and reduce arterial PCO_2 causing respiratory alkalosis. Approximately 28% of patients experience breathlessness (dyspnea) or an urge to breathe deeply with Adenoscan. These respiratory complaints are transient and only rarely require intervention.

Adenosine administered by inhalation has been reported to cause bronchoconstriction in asthmatic patients, presumably due to mast cell degranulation and histamine release. These effects have not been observed in normal subjects. Adenoscan has been administered to a limited number of patients with asthma and mild to moderate exacerbation of their symptoms has been reported. Respiratory compromise has occurred during adenosine infusion in patients with obstructive pulmonary disease. Adenoscan should be used with caution in patients with obstructive lung disease not associated with bronchoconstriction (e.g., emphysema, bronchitis, etc.) and should be avoided in patients with bronchoconstriction or bronchospasm (e.g., asthma). Adenoscan should be discontinued in any patient who develops severe respiratory difficulties.

PRECAUTIONS:

Drug Interactions

Intravenous Adenoscan has been given with other cardioactive drugs (such as beta adrenergic blocking agents, cardiac glycosides, and calcium channel blockers) without apparent adverse interactions, but its effectiveness with these agents has not been systematically evaluated. Because of the potential for additive or synergistic depressant effects on the SA and AV nodes, however, Adenoscan should be used with caution in the presence of these agents. The vasoactive effects of Adenoscan are inhibited by adenosine receptor antagonists, such as methylxanthines (e.g., caffeine and theophylline). The safety and efficacy of Adenoscan in the presence of these agents has not been systematically evaluated. The vasoactive effects of Adenoscan are potentiated by nucleoside transport inhibitors, such as dipyridamole. The safety and efficacy of Adenoscan in the presence of dipyridamole has not been systematically evaluated. Whenever possible, drugs that might inhibit or augment the effects of adenosine should be withheld for at least five half-lives prior to the use of Adenoscan.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate the carcinogenic potential of Adenoscan. Adenosine was negative for genotoxic potential in the Salmonella (Ames Test) and Mammalian Microsome Assay.

Adenosine, however, like other nucleosides at millimolar concentrations present for several doubling times of cells in culture, is known to produce a variety of chromosomal alterations. Fertility studies in animals have not been conducted with adenosine.

Pregnancy Category C

Animal reproduction studies have not been conducted with adenosine; nor have studies been performed in pregnant women. Because it is not known whether Adenoscan can cause fetal harm when administered to pregnant women, Adenoscan should be used during pregnancy only if clearly needed.

Pediatric Use

The safety and effectiveness of Adenoscan in patients less than 18 years of age have not been established.

Geriatric Use

Clinical studies of Adenoscan did not include sufficient numbers of subjects aged younger than 65 years to determine whether they respond differently. Other reported experience has not revealed clinically relevant differences of the response of elderly in comparison to younger patients. Greater sensitivity of some older individuals, however, cannot be ruled out.

ADVERSE REACTIONS:

The following reactions with an incidence of at least 1% were reported with intravenous Adenoscan among 1421 patients enrolled in controlled and uncontrolled U.S. clinical trials. Despite the short half-life of adenosine, 10.6% of the side effects occurred not with the infusion of Adenoscan but several hours after the infusion terminated. Also, 8.4% of the side effects that began coincident with the infusion persisted for up to 24 hours after the infusion was complete. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

Flushing	44%	Gastrointestinal discomfort	13%	Second-degree AV block	3%
Chest discomfort	40%	Lightheadedness/dizziness	12%	Paresthesia	2%
Dyspnea or urge to breathe deeply	28%	Upper extremity discomfort	4%	Hypotension	2%
Headache	18%	ST segment depression	3%	Nervousness	2%
Throat, neck or jaw discomfort	15%	First-degree AV block	3%	Arrhythmias	1%

Adverse experiences of any severity reported in less than 1% of patients include:

Body as a Whole: back discomfort; lower extremity discomfort; weakness.

Cardiovascular System: nonfatal myocardial infarction; life-threatening ventricular arrhythmia; third-degree AV block; bradycardia; palpitation; sinus exit block; sinus pause; sweating; T-wave changes, hypertension (systolic blood pressure > 200 mm Hg).

Central Nervous System: drowsiness; emotional instability; tremors.

Genital/Urinary System: vaginal pressure; urgency.

Respiratory System: cough.

Special Senses: blurred vision; dry mouth; ear discomfort; metallic taste; nasal congestion; scotomas; tongue discomfort.

Post Marketing Experience (see **WARNINGS**): The following adverse events have been reported from marketing experience with Adenoscan. Because these events are reported voluntarily from a population of uncertain size, are associated with concomitant diseases and multiple drug therapies and surgical procedures, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, (3) strength of causal connection to the drug, or a combination of these factors.

Body as a Whole: Injection site reaction

Central Nervous System: Seizure activity, including tonic clonic (grand mal) seizures, and loss of consciousness

Digestive: Nausea and vomiting

Respiratory: Respiratory arrest

OVERDOSAGE:

The half-life of adenosine is less than 10 seconds and side effects of Adenoscan (when they occur) usually resolve quickly when the infusion is discontinued, although delayed or persistent effects have been observed. Methylxanthines, such as caffeine and theophylline, are competitive adenosine receptor antagonists and theophylline has been used to effectively terminate persistent side effects. In controlled U.S. clinical trials, theophylline (50-125 mg slow intravenous injection) was needed to abort Adenoscan side effects in less than 2% of patients.

DOSAGE AND ADMINISTRATION:

For intravenous infusion only.

Adenoscan should be given as a continuous peripheral intravenous infusion.

The recommended intravenous dose for adults is 140 mcg/kg/min infused for six minutes (total dose of 0.84 mg/kg).

The required dose of thallium-201 should be injected at the midpoint of the Adenoscan infusion (i.e., after the first three minutes of Adenoscan).

Thallium-201 is physically compatible with Adenoscan and may be injected directly into the Adenoscan infusion set.

The injection should be as close to the venous access as possible to prevent an inadvertent increase in the dose of Adenoscan (the contents of the IV tubing) being administered.There are no data on the safety or efficacy of alternative Adenoscan infusion protocols.

The safety and efficacy of Adenoscan administered by the intracoronary route have not been established.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Rx only

Marketed by Astellas Pharma US, Inc.
Deerfield, IL 60015

Manufactured by Hospira Inc.
Lake Forest, IL 60045 USA

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The value of approved therapies for pulmonary arterial hypertension

Stuart Rich, MD *Chicago, IL*

Price is what you pay. Value is what you get.

Warren Buffett

In this issue of the Journal, Macchia et al[1] present the first meta-analysis of trials for pulmonary arterial hypertension (PAH). Their findings are startling, yet not surprising at the same time.

Meta-analyses can be very helpful in strengthening the power of small intervention effects and in providing guidance for future clinical trials with respect to the population enrolled, appropriate end points, and length of follow-up. One should also remember that meta-analyses taken from studies published in the literature potentially suffer from a negative publication bias because negative trials are often not published, and thus the meta-analyses oftentimes represent "the best of the best." In addition, if the clinical trials are widely heterogeneous with respect to the patient population under study, or by design, the conclusions may need to be tempered.

This article is particularly timely, given the recent approval of several medications for PAH, which is widely considered as a seriously disabling and fatal disease.[2] Currently, there are 7 medications approved for PAH worldwide, which are estimated to generate >1600 million dollars in revenue in 2007 (personal communication). Because PAH has now become among the most expensive diseases to treat in the world, it is certainly fair to ask if we are getting a fair "bang for our buck."

This meta-analysis included data from 16 randomized clinical trials extracted from the published literature, representing 3 different classes of approved therapies (prostacyclins, endothelin receptor blockers, and phosphodiesterase 5 inhibitors). One of the observations was the remarkable homogeneity among the studies. All but 1 of the trials included patients who had World Health Organization Category 1 PAH, and 70% of the patients were World Health Organization Functional Class 3. These studies were very homogeneous in design as well. Only 1 of the trials was >16 weeks in duration, all but 1 compared the active therapy against placebo, and half used a change in 6-minute walk distance (6MW) as the primary end point. A close look into the trials reveals that it was often the same centers, and same investigators, who enrolled patients into the studies.

The authors confirmed that a statistically significant increase in 6MW of 42.8 m occurred from active therapy. They also found a statistically significant improvement in functional class (33% on active therapy improved vs 15% of those receiving control). Whether these small intervention effects are clinically meaningful has been the subject of debate.[3-8] However, I think we can conclude from this analysis that the use of a vasodilator as therapy for PAH will predictably result in a small change in 6MW over a 12- to 16-week period irrespective of the drug used. Because patients who show marked vasoreactivity at the time of diagnosis are excluded from these trials, this response likely reflects that there exists a small pulmonary vasoconstrictive component in patients with PAH, which, when reversed, translates into a modest improvement in exercise tolerance. Because it appears that this phenomenon has now been firmly proven, there seems to be little need for any more vasodilator trials of this sort.

More importantly, there was no survival benefit realized from these therapies. In addition, although patients with worse 6MW tests at baseline had worse survival, the authors were unable to show any association between the change in 6MW and improved survival. In fact, the CIs revealed a mortality effect ranging from a 30% reduction to a 22% increase. Their startling conclusion is that the approved therapies of PAH have yet to demonstrate an impact on survival in this highly fatal illness and that the data fail to validate that the widely accepted 6MW is an adequate surrogate end point for this disease.

The treatment of PAH has had an interesting history. The use of calcium-channel blockers as first-line therapy in a subset of patients found to be highly vasoreactive at the time of diagnosis is widely accepted by expert opinion and evidence-based guidelines as an important treatment of this disease.[9] There has never been a long-term randomized clinical trial using calcium blockers for PAH, but the prospective observational reports that used

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survival as an end point have shown a dramatically improved survival over historical controls and published registries.[10,11] Of note is that the report of the long-term benefits of calcium-channel blockers was not published until 5-year follow-up was available, citing a concern that "it remains unknown whether this response will persist indefinitely."[10] Fortunately, calcium blockers are widely available and inexpensive.

Compare that with the approved medications, which in trials have consistently shown small changes in 6MW with therapy, an end point that has never been validated, and one that can more improve with an exercise rehabilitation program.[12] They also produce trivial changes in hemodynamics and no effect on survival with the sole exception of intravenous epoprostenol in critically ill patients over 12 weeks.[13] In addition, for some reason we continue to ignore the prodigious results from the Beraprost Study Group,[14] which conducted the only randomized clinical trial evaluating a treatment of pulmonary hypertension for 1 year. That study showed a 3-month improvement in 6MW comparable to what has been achieved with all the other approved therapies, which then vanished by the end of a year.

The possibility that therapies for PAH may have no beneficial long-term efficacy may seem incredulous to some. However, those of us with gray hair vividly remember the observations mentioned by Macchia et al[1] about the disconnect between improving ejection fraction and mortality in patients with heart failure and between the reduction of ventricular arrhythmias and arrhythmic deaths in patients with coronary artery disease. This could be déjà vu all over again.

To me, the message from this meta-analysis is that the time has come for a major change in the design of clinical trials evaluating the treatment of PAH. I believe that any future trial of therapies seeking approval for PAH should be at least 1 year in duration and should use survival as the primary end point. It is unlikely that the pharmaceutical industry will voluntarily propose this, and it is unlikely that the physicians who sit on the steering committees of the trials will insist on it. This leaves me then to appeal to the regulatory authorities who can and should demand that our approach toward developing new therapies for PAH undergo a major overhaul.

There are currently 10 new therapies for PAH in various stages of clinical development, promising to be as expensive as their predecessors. For many of these therapies, the same clinical trial design appears to have been adopted, making it unlikely that we will learn anything new about the treatment of this devastating disease. All of this makes me wonder that when it comes to the treatment of PAH with the many approved and expensive therapies, we may have "bought the farm."

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Current concepts in the mechanisms and management of drug-induced QT prolongation and torsade de pointes

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Drug-induced long QT syndrome is characterized by a prolonged corrected QT interval (QTc) and increased risk of a polymorphic ventricular tachycardia known as torsade de pointes (TdP). We review mechanisms, predispositions, culprit agents, and management of this potentially fatal phenomenon. Virtually all drugs that prolong QTc block the rapid component of the delayed rectifier current (I_{kr}). Some drugs prolong QTc in a dose-dependent manner, others do so at any dose. Most patients that develop drug-induced TdP have underlying risk factors. Female sex is the most common. Implicated drugs include class 1A and III antiarrhythmics, macrolide antibiotics, pentamidine, antimalarials, antipsychotics, arsenic trioxide, and methadone. Treatment for TdP includes immediate defibrillation for hemodynamic instability and intravenous magnesium sulfate. Potassium levels should be maintained in the high normal range, and all QT prolonging agents must be promptly discontinued. (Am Heart J 2007;153:891-9.)

Drug-induced long QT syndrome (LQTS) is characterized by acquired QT interval prolongation and increased risk of torsade de pointes (TdP). In 1964, Selzer and Wray[1] reported QT prolongation and ventricular fibrillation (VF) in response to quinidine. Two years later, Dessertenne[2] described TdP, a polymorphic ventricular tachycardia where QRS complexes 'twist' around an isoelectric line in a sinusoidal fashion (Figure 1). Symptoms of TdP include palpitations, syncope, and seizure-like activity. Torsade de pointes is usually self-limited but may degenerate into VF and cause sudden cardiac death. A variety of medications have been implicated in drug-induced LQTS. QT prolongation and TdP are the most common reasons pharmaceuticals are restricted or removed from the US market.[3] We review mechanisms, predispositions, culprit agents, and management of this potentially fatal phenomenon.

QT measurement

The QT interval is the electrocardiographic (ECG) manifestation of ventricular depolarization and repolarization. It is measured from QRS complex onset to T wave termination (Figure 2). Longest QT intervals are generally measured in precordial leads. V3 or V4 appear most reliable for assessing QT prolongation.[4] QT intervals may vary due to diurnal effects, electrolyte imbalance, autonomic fluctuations, ECG acquisition technique, as well as intra- and interobserver variability.[5,6] One study suggested that whites have longer QT intervals than African Americans.[7] We were unable to confirm this finding.[8] QT intervals normally shorten with tachycardia and lengthen with bradycardia. Therefore, a rate corrected QT (QTc) interval should be calculated. In 1920, Bazett[9] proposed a formula dividing the longest QT interval by the square root of the RR interval (Figure 2). Although there is no consensus *best* QTc method, Bazett's formula remains the gold standard. This formula may overestimate drug-induced QT prolongation.[10] QTc intervals <440 milliseconds are clearly normal. Intervals of 440 to 460 milliseconds in men and 440 to 470 milliseconds in women are considered borderline.[11] Most authorities agree women have longer QTc intervals.

Molnar et al[6] demonstrated circadian QTc variation of 95 ± 20 milliseconds with longest intervals recorded during sleep. Although variability is expected, any QTc prolongation to the abnormal range should alert physicians to a risk of TdP.

The appropriate method for measuring QTc during atrial fibrillation is unclear. QTc may be measured over 10 consecutive beats and averaged. Alternatively, QTc following shortest and longest RR intervals may be averaged.[12] There are no data to guide QTc calculation in the setting of QRS prolongation. Some authors have proposed ignoring the QRS and measuring the JT

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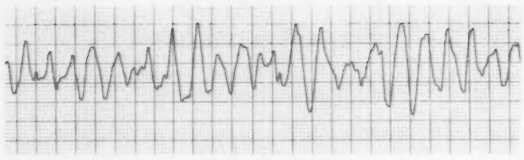
Figure 1



Example of TdP in a lead II rhythm strip. This patient was taking high-dose methadone, and his rhythm quickly degenerated to VF.

interval (as an index of ventricular repolarization).[13] However, evidence suggests the JT interval is dependent on QRS duration, and there are no consensus normal JT values.[14] In an attempt to standardize QT measurement, an expert panel proposed the guidelines noted in Table I.[15]

Mechanisms of QT prolongation and TdP

Myocardial repolarization is primarily mediated by efflux of potassium ions. Two subtypes of the delayed rectifier K^+ current, I_{kr} (rapid) and I_{ks} (slow), are predominantly responsible for repolarization. Virtually all drugs that prolong QTc block I_{kr}.[16] De Bruin et al[17] demonstrated strong correlation between a drug's ability to block I_{kr} and its potential to cause ventricular arrhythmias and sudden death. I_{kr} blockade causes a delay in phase 3 rapid repolarization of the action potential (Figure 3). Increased action potential duration is reflected by QT prolongation. Repolarization delays may also distort T waves or produce prominent U waves.

Prolonged repolarizatrion may cause early afterdepolarizations (EADs) due to activation of inward depolarizing currents, most likely L-type calcium channels or sodium-calcium exchange current (I_{NCX}).[18] Early afterdepolarizations appear as depolarizing oscillations in membrane voltage during phases 2 and 3 of the action potential (Figure 4). Early afterdepolarizations that reach threshold voltage cause ventricular extrasystoles. Purkinje fibers and M cells (midmyocardial) are especially susceptible to drug-induced QT prolongation, EADs, and ventricular extrasystoles.[20] Heterogeneity in ventricular repolarization (dispersion of refractoriness) can create zones of unidirectional block. Repetitive extrasystoles (triggered activity), unidirectional block, and zones of slow conduction can lead to reentry and TdP.[18]

Drug-induced TdP is usually preceded by a short-long-short ECG sequence (Figure 5).[22] This generally starts with one or more premature ventricular complexes followed by a compensatory pause. The subsequent sinus beat may have an especially long QT and deformities of T or U waves. This sinus beat is followed by another premature ventricular complex that precipitates TdP. The period near the T wave peak where premature stimuli may induce ventricular arrhythmias is known as the vulnerable period.[23]

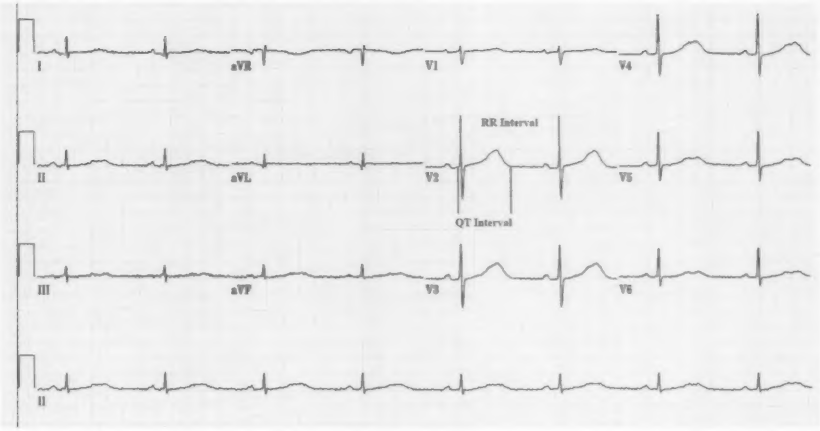
Many patients with marked QT prolongation never develop TdP, although others develop TdP with minimal prolongation. Several other ECG variables have been investigated as predictors of TdP. QT dispersion, the difference between maximum and minimum QT intervals, was postulated to be a more direct measure of spatial heterogeneity of repolarization.[24] However, QT dispersion is mostly dependent on T wave morphology (width, amplitude, and axis) and does not accurately predict drug-induced TdP.[25] Tpeak-Tend measurement, suggested as a measure of transmural dispersion of repolarization, needs prospective validation.[20] Manifest T wave alternans (beat to beat alternation in amplitude or polarity), a harbinger of instability in congenital LQTS, is rare in acquired LQTS and may not have the same implications (Figure 6).[21] Microvolt T wave alternans predicts susceptibility to ventricular arrhythmias.[26] Its use in predicting drug-induced TdP remains unclear. Despite lack of specificity, QT prolongation remains the most useful clinical variable to predict risk of TdP.

Risk factors

Most patients treated with QT prolonging medications never develop TdP. Several risk factors predispose patients to drug-induced LQTS and TdP. Zeltser et al[27] reviewed 249 incidents of TdP due to noncardiac medications. Virtually all patients had 1 risk factor, and 71% had multiple risk factors. Female sex, the most common risk, was present in 71%. Other common risk factors included structural heart disease (myocardial infarction, heart failure, valvular disease, or cardiomyopathy), hypokalemia, multiple QT prolonging drugs or agents interfering with their metabolism, higher-than-average drug dosage, prolonged baseline QTc (≥450 milliseconds), family history of congenital LQTS, and prior drug-induced TdP. Hepatic impairment, bradycardia, and atrioventricular block also increase the risk of TdP.[22]

Subclinical mutations in genes causing congenital LQTS have been found in patients with medication-induced QT prolongation and ventricular arrhythmias.[28-30] Patients with congenital LQTS 6 (mutations in the gene encoding the β subunit of I_{kr}) generally do not have arrhythmias in the absence of provocation. Yang et al[31] found that 10% to 15% of patients with drug-related TdP had mutations or polymorphisms in one of the long QT genes. One mutation, S1103Y, in the cardiac sodium channel gene SCN5A has been primarily identified in African Americans (13.2%).[32] One white family with this mutation has also been reported.[33] The concept of repolarization reserve (variable redundancy of repolarizing currents) may

Figure 2



QTc = QT interval ÷ √RR interval.

explain why some patients with mutant genes do not develop QT prolongation or TdP until additional insults further limit repolarization.[34]

QTc prolonging medications

Some medications prolong QTc and induce TdP in a dose-dependent manner. Others may precipitate TdP at any dose resulting in potassium channel blockade (see below). We will review specific agents that prolong QTc and cause TdP (Table II). Several are metabolized by the Cytochrome P450 3A4 (CYP3A4) system. Familiarity with agents that inhibit this system is critical (Table III).[35]

Antiarrhythmics

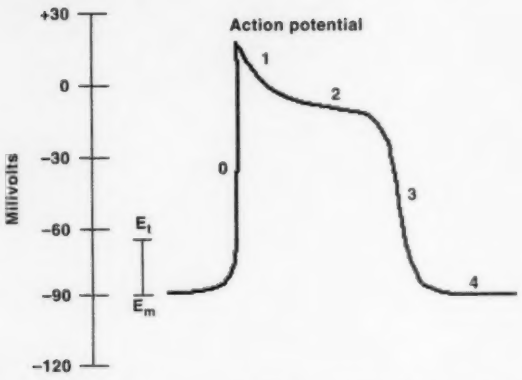
Torsade de pointes is most commonly caused by antiarrhythmic medications. Patients taking these commonly have organic heart disease and often take diuretics that cause hypokalemia and hypomagnesemia. Class IA drugs (quinidine, disopyramide, procainamide) block outward K^+ currents and inward Na^+ currents. Na^+ current blockade increases as serum levels increase. K^+ current blockade predominates at low serum levels. Therefore, TdP frequently occurs at low or subtherapeutic serum levels.[36] The risk of TdP from quinidine is approximately 1.5%.[37] Disopyramide has also been implicated.[38] Procainamide is less likely to cause TdP. Its metabolite, *N*-acetylprocainamide, has potent I_{kr} blocking properties that may result in QT prolongation and TdP.[39] This is particularly important in patients with impaired renal function who may develop high *N*-acetylprocainamide levels.

Table I. Guidelines for QT measurement

1. Measurements should be:
   (a) Made manually from a 12-lead ECG
   (b) Done from beginning of QRS complex to end of the T wave
   (c) Averaged over 3 to 5 beats in a single lead
2. Prominent U waves should be included in the measurement if they merge into the T wave
3. QT should be assessed during peak plasma concentration of QT prolonging substance
4. QT should be corrected for heart rate

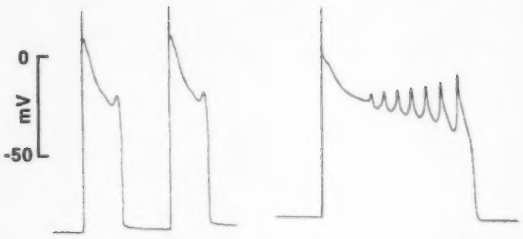
Unlike class IA agents, class III antiarrhythmics (potent I_{kr} blockers) prolong QTc in a dose-dependent manner. Dofetilide, ibutilide, and sotalol, which are class III drugs that pose the highest risk, progressively prolong QTc as serum levels increase.[22,38] These drugs block I_{kr} most effectively at low heart rates, a phenomenon known as *reverse use dependence*. Therefore, risk of TdP increases with bradycardia. For sotalol, TdP risk ranges from 0.8% to 3.8%.[38] Similar rates (0.9% to 3.3%) have been reported with dofetilide.[40,41] Intravenous ibutilide has caused TdP in 3.6% to 8.3% of patients when administered for conversion of atrial fibrillation or atrial flutter.[42,43] Amiodarone is unlikely to cause TdP despite significant QT prolongation. The incidence of TdP at currently used doses is <1%.[44,45] In addition to blocking I_{kr} without reverse use dependence, amiodarone prolongs action potential duration in a homogenous manner, reducing heterogeneity of refractorinesis and making the myocardium less susceptible to reentry.[46] Additional electrophysiologic

Figure 3



Representation of a myocardial action potential. Phase 0 rapid depolarization is mediated by sodium entry into cells. Phase 1 and 3 repolarization results from potassium efflux from cells. Balanced slow calcium entry and potassium exit cause the plateau in phase 2. Potassium reenters and sodium exits cells during phase 4 recovery. Adapted with permission from Arnsdorf, M, Lee, P. Myocardial action potential and action of antiarrhythmic drugs. In: UpToDate, Rose, BD (Ed), *UpToDate*, Waltham, MA 2006. For more information visit www.uptodate.com.

Figure 4



Action potential recordings showing early EADs. The panel on the left depicts single EADs, whereas the one on the right depicts multiple EADs from progressively more negative transmembrane potential. Reprinted with permission from El-Sherif et al.[19]

effects that help explain its safety include noncompetitive β antagonism and inward L-calcium channel blockade (which may reduce EADs).[42]

Unlike other calcium channel blockers, Bepridil prolongs QTc and has been associated with TdP.[47,48] It can block I_{NCX} and possesses class 1A properties.[49] Bepridil was removed from the US market in 2003.

Promotility medications

Cisapride, used to treat esophageal reflux, causes high affinity I_{kr} blockade and has been among the most common agents implicated in TdP. Between 1993 and 1999, the Food and Drug Administration received 341 reports of QT prolongation, ventricular arrhythmia, or cardiac arrest related to cisapride.[50] Cisapride marketing, in the United States, was stopped in July 2000.

Antimicrobials

The macrolide antibiotics erythromycin and clarithromycin have been implicated in sudden death due to TdP.[51,52] Proarrhythmia may be precipitated by I_{kr} blockade. In addition, these drugs are metabolized by and inhibit CYP3A4.[53] They are especially dangerous for patients receiving another CYP3A4 inhibitor or a QT prolonging medication metabolized by CYP3A4 (Table III). Although TdP with azithromycin has been reported, its arrhythmogenic potential is well below erythromycin or clarithromycin.[54,55]

Sporadic incidents of TdP have been reported with fluoroquinolone antibiotics. The overall incidence of fluoroquinolone-induced TdP is very low. Sparfloxacin, resulting in the greatest action potential prolongation, has been removed from the US market.[56] There is no evidence that currently available fluoroquinolones cause TdP without underlying risk factors.[57,58]

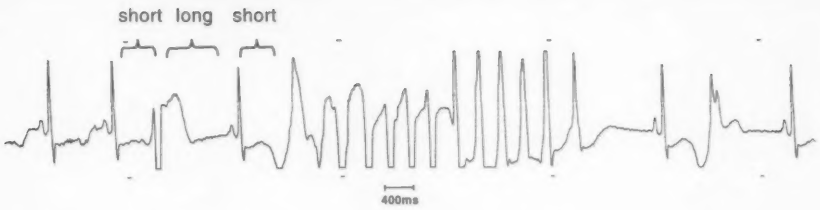
QT prolongation and TdP have been noted with pentamidine, an antiprotozoal, antifungal drug used to treat parasitic infections and *Pneumocystis carinii* pneumonia.[59] Pentamidine-induced QT prolongation is related to reduction in available I_{kr} channels.[60] Although case reports describe TdP in patients receiving other systemic antifungals (fluconazone, itraconazole, ketoconazole, and voriconazole), these are unlikely to cause TdP without preexisting risk factors.[61]

Antimalarials have been associated with QT prolongation and TdP.[62] Halofantrine and chloroquine are the most potent I_{kr} inhibitors. Torsade de pointes risk is highest with halofantrine.[63,64] These drugs are frequently used around the world, and TdP incidence is likely underreported.

Psychiatric drugs

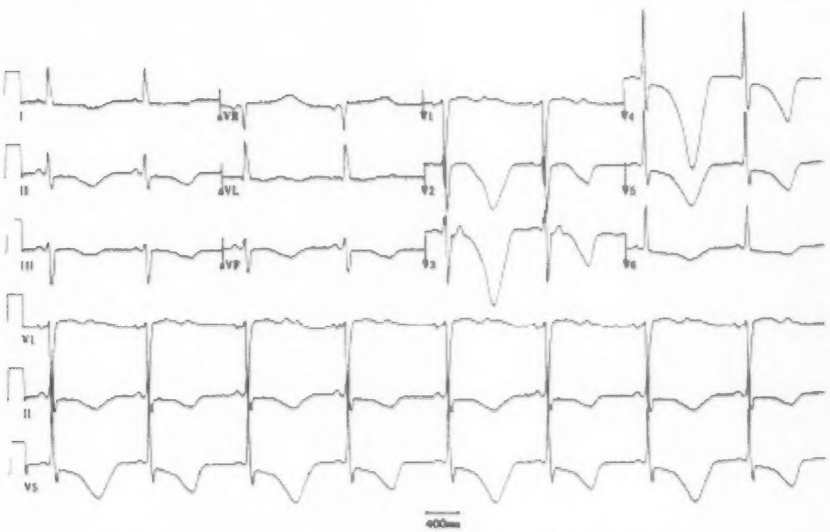
Dose-dependent QT prolongation has been observed with antipsychotic medications.[65] Phenothiazine (thioridazine, chlorpromazine, and mesoridazine), butyrophenone (droperidol and haloperidol), and diphenylpiperidine (pimozide) neuroleptics have all been associated with TdP.[66-69] In 495 patients receiving psychiatric medications, 8% had QT prolongation.[70] Thioridazine and droperidol posed the highest risk. Both have been shown to block I_{kr} in animal models.[71,72]

Figure 5



Characteristic short-long-short sequence preceding a short run of TdP in a patient on high-dose procainamide and amiodarone. Adapted with permission from Trohman and Sahu.[21]

Figure 6



Twelve-lead ECG depicting manifest T wave alternans in a patient who had drug-induced TdP. The T wave alternans occurred "paradoxically" after the ventricular arrhythmias had stabilized. Adapted with permission from Trohman and Sahu.[21]

QT prolongation has also been noted with tricyclic antidepressants. Torsade de pointes is primarily limited to patients with additional risk factors.[73]

Miscellaneous medications

Arsenic trioxide, which is used to treat promyelocytic leukemia, has been associated with a very high rate of QT prolongation.[74,75] In 99 patients treated with arsenic trioxide, 38% developed significant QT prolongation; however, only 1 patient developed TdP.[75] The high incidence of QT prolongation but low risk of TdP may be explained by its unique electrophysiologic properties.[76,77] In addition to blocking I_{kr}, I_{ks} and reducing surface expression of I_{kr} channels, arsenic appears to activate a current ($I_{k\text{-}ATP}$) that promotes repolarization and decreases the arrhythmic milieu.

Methadone, a long-acting synthetic opiate, is widely used and considered safe, effective treatment for heroin addiction and chronic pain. However, methadone blocks I_{kr} and prolongs QTc in a dose-dependant fashion.[78,79] Fifty-nine cases of methadone-induced LQTS or TdP

Table II. Drugs implicated in TdP

1. Antiarrhythmic medications
   - Class IA
     - Quinidine
     - Procainamide (metabolized to *N*-acetylprocainamide)
     - Disopyramide
   - Class III
     - Dofetilide
     - Ibutilide
     - Sotalol
     - Amiodarone
   - Class IV
     - Bepridil*
2. Promotility medications
   - Cisapride*
3. Antimicrobial medications
   - Macrolides
     - Erythromycin
     - Clarithromycin
   - Fluoroquinolones
     - Sparfloxacin*
   - Antiprotozoals
     - Pentamidine
   - Antimalarials
     - Halofantrine
     - Chloroquine
4. Antipsychotic medications
   - Phenothiazine neuroleptics
     - Thioridazine
     - Chlorpromazine
     - Mesoridazine
   - Butyrophenone neuroleptics
   - Droperidol
   - Haloperidol
     - Diphenylpiperidine neuroleptics
   - Pimozide
5. Miscellaneous medications
   - Arsenic trioxide
   - Methadone
6. Vitamins, supplements, and herbal medications
   - Cesium
   - Licorice
   - Zhigancao

*Unavailable or severely limited availability in the United States.

Table III. Inhibitors of CYP3A4

1. Antihypertensive medications
   - Dihydralazine
   - Diltiazem
   - Mibefradil*
   - Nicardipine
   - Verapamil
2. Anticancer medication
   - Irinotecan
3. Antidepressant and anxiolytic medications
   - Fluoxetine
   - Midazolam
4. Antimicrobial medications
   - HIV agents
     - Amprenavir
     - Delavirdine
     - Nelfinavir
     - Ritonavir
   - Macrolides
     - Clarithromycin
     - Erythromycin
     - Troleandomycin
   - Tuberculosis agent
     - Isoniazid
5. Endocrine medications
   - Contraceptives
     - Ethinylestradiol
     - Gestodene
   - Antiprogesterone agent
     - Mifepristone
   - Estrogen receptor modulators
     - Raloxifene
     - Tamoxifen
5. Food and herbal constituents
   - Bergamottin (grapefruit juice)
   - Glabridin (licorice)
   - Oleuropein (olive leaf)
   - Resveratrol (red grape skin)

*Unavailable or severely limited availability in the United States.

were reported to the Food and Drug Administration between 1969 and 2002.[80] An additional risk factor was found in 75% of these cases.

Vitamins, supplements, and herbals

Torsade de pointes has been described in patients taking nutritional or herbal supplements. Cesium, which is used to treat or prevent cancer, induces EADs and prolongs QTc. It has been used experimentally to mimic LQTS.[81] Torsade de pointes has been reported in patients taking cesium.[82-84] Licorice and zhigancao (a chinese herbal prepared from licorice), which is used to treat dyspepsia and peptic ulcer disease, cause hypokalemia and have been associated with TdP.[85-87] Extracts from licorice, grapefruit juice, olive leaves, and red grape skins inhibit CYP3A4 and may interfere with metabolism of QT prolonging medications (Table III). Corn silk, dandelion, juniper, and uva-ursi have diuretic properties and may potentiate arrhythmias if hypokalemia occurs.[88]

Recommendations

It is impractical (perhaps impossible) for patients and clinicians to memorize all medications implicated in QT prolongation. The University of Arizona (Arizona-CERT) maintains a database of QT prolonging drugs. This list, stratified by relative risk, can be accessed via the internet (www.torsades.org, www.qtdrugs.org, www.longqt.org, www.sads.org).

Our discussion of electrophysiologic mechanisms has been intentionally brief. Readers should refer to the consensus statement from Fenichel et al[89] and a review by Yap and Camm[22] for greater detail.

Despite limitations, treatment with QT prolonging medications is frequently necessary. Risks of therapy must be weighed against benefits. Alternative treatments should be considered. Underlying risk factors should be assessed, and reversible conditions must be corrected before drug initiation. Polypharmacy (multiple QT prolonging medications or agents that interfere with their metabolism) should be avoided. Patients should be counseled about proarrhythmic risk.

Great caution is necessary when initiating class III antiarrhythmics. Patients are routinely hospitalized for at least 72 hours during dofetilide initiation. Ibutilide should be administered while the patient is hospitalized in a telemetry unit. A monitoring period of at least 4 hours post ibutilide is recommended. Hospitalization for sotalol initiation is controversial. Patients with underlying risk factors should be hospitalized and monitored.[90,91]

Treatment

Intravenous magnesium sulfate (2 g bolus followed by an infusion of 2-4 mg/minute) is the initial therapy of choice regardless of serum level.[92] If sustained, hemodynamically unstable polymorphic ventricular tachycardia or VF develops, immediate nonsynchronized defibrillation is indicated. Serum potassium should be maintained in the high-normal range (4.5-5 mmol/L). QT prolonging medications and drugs interfering with their metabolism must be promptly discontinued.

Overdrive transvenous pacing shortens QTc and is highly effective in preventing recurrence.[93] It is especially useful in cases refractory to magnesium or when TdP is precipitated by a pause or bradycardia. Short-term pacing rates of 90 to 110 beats/min are generally used. Experience with permanent pacemakers suggests rates >70 beats/min protect against drug-induced TdP.[94,95]

Isoproterenol, titrated to a heart rate ≥90, is useful if temporary pacing is unavailable or while preparing for transvenous catheter insertion.[96] Isoproterenol is contraindicated in patients with congenital LQTS or ischemic heart disease.

Long-term treatment involves avoidance of offending agents. Conditions that predispose to electrolyte imbalance must be corrected. In patients with sick sinus syndrome or atrioventricular block and bradycardia or pause-dependent drug-induced TdP, permanent pacing with programmable pause prevention algorithms (such as rate smoothing) may be indicated.[97]

Conclusions

Drug-induced LQTS remains an important, potentially preventable source of morbidity and mortality. Many unrelated drugs may lengthen QTc and cause TdP, usually via I_{kr} blockade. The list of these agents is constantly evolving. Clinicians and patients must be familiar with resources providing comprehensive information. Predisposing risk factors and drug-drug interactions should be considered. If drug-induced TdP develops, prompt treatment is critical and may be life saving.

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Beyond the platelet count: Heparin antibodies as independent risk predictors

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A major potential side effect of heparin is immunogenicity, eliciting antibody development to a protein complex comprised of platelet factor 4 and heparin. Nevertheless, the clinical implications of heparin antibody positive patients remain broad, ranging from no apparent clinical consequences to life-threatening arterial and venous thromboemboli. The "Iceberg Model" has been proposed to depict this spectrum, with a relatively large population of antibody-positive patients forming the base of the iceberg, a smaller population of thrombocytopenic patients in the middle and a limited number of patients with thrombocytopenia and thrombosis comprising the apex. An underlying assumption of this model is that thrombosis occurs only in settings of relative or absolute thrombocytopenia. However, several recent studies suggest that antibody formation to platelet factor 4/heparin complexes, even in the absence of thrombocytopenia, may be associated with thrombotic events. In this review, we summarize these data, consider potential mechanisms for thrombosis, and suggest recommendations for testing and management of antibody-positive patients. (Am Heart J 2007;153:900-6.)

Heparin-induced thrombocytopenia (HIT) is an immune-mediated drug reaction occurring in as many as 5% of patients exposed to extended therapy with unfractionated heparin. In contrast to other drug-induced thrombocytopenias, HIT is characterized by platelet activation and risk for both venous and arterial thromboses. Recent evidence suggests that immune complexes composed of IgG antibody, platelet factor 4 (PF4), and heparin bind to Fc γ receptors on the platelet surface to produce platelet activation.[1] Although platelet activation alone may account for prothombotic conditions associated with HIT, accumulating evidence suggests that anti-PF4/heparin antibodies also bind and "activate" vascular endothelium, monocytes, and macrophages to express tissue factor.[2] Patients receiving heparin who develop HIT experience increases in both relative and absolute risks for thrombosis (odds ratio [OR] 20-40, absolute risk 30%-75%).[1] Heparin-induced thrombocytopenia usually occurs 5 to 14 days after initiating heparin therapy; however, in patients with prior exposure, thrombocytopenia and/or thrombotic complications may occur within 12 hours.[3,4] Heparin-induced thrombocytopenia remains a clinical diagnosis with laboratory testing, providing a confirmatory role.[5] Most often, HIT is diagnosed in the setting of relative or absolute thrombocytopenia after exposure to heparin. Accompanying thrombosis may or may not be present. Laboratory-based assays are applied in a confirmatory role and usually consist of 1 of 2 types of assessments for anti-PF4/heparin antibodies: (1) functional assays (eg, serotonin release assay or heparin-induced platelet aggregation) or (2) solid-phase enzyme-linked immunosorbent assays (ELISA) that quantitate concentration of antibodies directed against PF4/heparin or PF4/polyanion complexes. Immunoassays provide greater sensitivity but lower specificity than functional assays for confirmatory diagnosis of HIT—arising in part from ELISA detection of IgA and IgM antibodies that are less efficient at inducing platelet activation and a prothrombotic state. Accordingly, some investigators have suggested that ELISA-based detection of anti-PF4/heparin antibodies leads to overdiagnosis of HIT.[6,7] However, recent literature suggests that laboratory-based diagnosis of anti-PF4/heparin antibodies independently predicts for adverse outcomes even in the absence of thrombocytopenia or a clinical diagnosis of HIT.

Tables I and II display the unadjusted ORs (or hazard ratio [HR], where appropriate) for each considered study. Because some studies originally adjusted the event rates for background risk factors, whereas others did not, the unadjusted OR may be different from that in the original report but now reflect the independent effect of antibody status on outcome. The event rates on which the calculations are based are provided in the

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Table I. Acute coronary syndrome or cardiac surgery patients with anti-PF4/heparin antibodies in absence of HIT

Study	Population	Outcome	Events by Ab status*		OR†	95% CI	P
			Ab+	Ab−			
Mattioli et al[8]	124 Consecutive patients with unstable angina treated with UFH	Combined end point of death, MI, recurrent angina, stroke, urgent revascularization in 1 y	66% (25/38)	44% (38/86)	2.4	1.1-5.4	.02
Williams et al[9]	218 Patients enrolled in GUSTO-IV–ACS trial, likely to have had heparin exposure	Death or MI	30% (7/23)	11% (22/195)	3.4	1.3-9.3	.02
		MI alone (30-d outcomes)	22% (5/23)	6% (12/195)	4.2	1.3-13.4	.01
Matsuo et al[10]	248/254 Japanese patients with ACS treated with UFH	Combined end point of thromboembolic events (MI, coronary stent thrombosis, ischemic stroke, intracardiac thrombosis)	28% (5/18)‡	3% (6/230)‡	14.4‡	3.9-53.3‡	.0004
Gluckman et al[11]	101 of 154 Patients presenting for elective or urgent PCI	Combined end points of death, MI, revascularization, noncardiac thromboembolic events at 6-m follow-up	13% (3/23)	14% (11/78)	0.91	0.2-3.6	.90
Bennett-Guerrero et al[12]	466 Patients undergoing CABG, valve surgery, or both	Primary end point of combined death and postoperative length of stay >10 d	34% (20/59)	22% (88/407)	1.9	1.03-3.3	.04

Ab, Antibody; *UFH*, unfractionated heparin; *CABG*, coronary artery bypass graft.
*Numerator indicates number of patients with specified outcome; denominator represents number of antibody positive or antibody negative patients.
†Odds ratios and 95% CIs calculated on unadjusted event rates (shown) and may differ from original report.
‡Data from publication reanalyzed to exclude patients with HIT.

tables as well as 95% CIs around these estimates. Significance values are calculated using χ^2 or Fisher exact test, as appropriate.

Heparin antibody–positive cardiac patients without HIT

There have been 5 reports of the consequences of anti-PF4/heparin antibodies in nonthrombocytopenic patients with acute coronary syndrome (ACS) and those undergoing cardiac surgery (Table I). Mattioli et al[8] studied 124 patients with unstable angina who were treated with unfractionated heparin. At 1 year of follow-up, the combined outcome of death, myocardial infarction, urgent revascularization, and stroke occurred in 66% of the antibody-positive patients, as compared with 44% of those who were antibody-negative (P = .02). Williams et al[9] studied a selected group of patients from the GUSTO IV–ACS trial. Patients testing positive for anti-PF4/heparin antibodies were 4 times more likely to experience death or myocardial infarction (MI) (P = .02) or MI alone (P = .01) within 30 days even after accounting for covariates by logistic regression analysis. Matsuo et al[10] reported similar findings in a group of 254 Japanese patients with ACS. There was a 28% likelihood of thromboembolic events in subjects testing positive for anti-PF4/heparin antibodies, as compared with only 3% incidence in those without antibodies (P = .0004). In contrast, the fourth study by Gluckman et al[11] found no statistically significant increase in thrombotic events in antibody-positive patients. This study analyzed patients undergoing elective as well as urgent percutaneous coronary intervention (PCI). As the authors of this study note,[11] the negative findings may be attributable to more aggressive medical therapy, including uniform use of glycoprotein IIb/IIIa inhibitors during the PCI as well as prolonged therapy with adenosine diphosphate receptor antagonists. Furthermore, the inclusion of patients undergoing elective PCI may have reduced the likelihood of adverse events in antibody-positive patients.

A single study by Bennett-Guerrero et al[12] has evaluated the prognostic significance of anti-PF4/heparin antibodies in 466 patients undergoing coronary artery bypass grafting, valve surgery, or both. The primary end point of their study included in-hospital death or a postoperative hospital length of stay exceeding 10 days. The authors found that the primary end point occurred in 34% of subjects testing positive for anti-PF4/heparin antibodies, as compared to 22% of those who were antibody-negative (P = .04). Furthermore, the length of hospital stay was significantly longer in those testing positive for anti-PF4/heparin antibodies preoperatively.

Heparin antibody–positive noncardiac patients without HIT

Outside the cardiology arena, there have been several other reports of the prognostic significance of

Table II. Noncardiac patients with anti-PF4/heparin antibodies in absence of HIT

Study	Population	Outcome	Events by Ab status* (ELISA absorbance)		OR/(HR)†	95% CI	P
Peña de la Vega et al[14]	57 Patients with ESRD undergoing hemodialysis	All-cause mortality	2.5-fold increased risk in 19 patients in highest tertile of Ab absorbance		(2.5)	1.07-5.72	.03
		Cardiovascular death (mean follow-up of 798 d)	4.1-fold increased risk in 19 patients in highest tertile of Ab absorbance		(4.1)	1.32-13.00	.02
Yu et al[15]	100 Consecutive chronic hemodialysis patients	Thrombosis or need to change vascular access within 1 y	Higher Ab absorbance (0.202) in 32 patients in thrombosis and access change group vs 68 not in group (0.161)		NA	NA	.03 in thrombosis group, .04 in access change group
			(Ab+)‡	(Ab−)‡			
Lindhoff-Last et al[16]	1076 of 1137 plasma samples of DVT patients in CORTES trial	Thromboembolic complications PE	8/119 (7%)§	27/953 (3%)§	2.5§	1.1-5.6§	.048§
			4/119 (3%)§	10/953 (1%)§	3.3§	1.0-10.6§	.06§
Calaitges et al[17]	106 Patients with vascular disease undergoing elective arterial reconstructive surgery	Postoperative thrombotic events, including MI within 30 d	18% (4/22)	7% (6/84)	2.9	0.74-11.3	.21
Lindhoff-Last et al[18]	50 Patients with arterial occlusive disease or AAA admitted for vascular surgery	Venous or arterial thrombosis during hospitalization	10% (3/30)	5% (1/20)	2.1	0.2-21.9	.64
Warkentin et al[19]	Representative subgroup of 381/665 patients undergoing orthopedic surgery, randomized to UFH or LMWH prophylaxis	Thrombotic complications (DVT or PE)	21% (3/14)	17% (63/367)	1.3	0.36-4.9	.72

ESRD, End stage renal disease; *NA*, not applicable; *DVT*, deep venous thrombosis; *AAA*, abdominal aortic aneurysm; *PE*, pulmonary embolism.
*Antibody status was indicated either by absorbance value in the ELISA assay or by a threshold value, with positive (Ab+) and negative (Ab−) test results.
†Odds ratios, HR, and 95% CIs calculated on unadjusted event rates (shown) and may differ from original report.
‡Numerator indicates number of patients with specified outcome; denominator represents number of antibody positive or antibody negative patients.
§Data from publication reanalyzed to exclude patients with HIT.

anti-PF4/heparin antibodies (Table II). Thrombotic events have been noted in antibody-positive patients undergoing arterial reconstructive surgery,[13] hemodialysis,[14,15] and treatment for venous thromboembolic disease.[16] However, other studies of patients undergoing vascular surgery[17,18] or venous thromboembolism prophylaxis[19] have failed to find an increased event rate in antibody-positive patients. Overall, the occurrence of thrombotic events in noncardiac patients appears less prevalent than in cardiac patients. Although further studies are necessary to explore this apparent difference, it is possible that the more overt clinical presentation of recurrent arterial thrombotic events in patients being monitored for ACS explains the higher event rates in this group. As discussed below, it is also possible that cardiac patients have certain specific risk factors (such as hypercholesterolemia) that predispose to recurrent events in the presence of heparin antibodies.

Possible mechanisms

There are several potential mechanisms by which anti-PF4/heparin antibodies might induce adverse events in nonthrombocytopenic (ie, non-HIT) patients (Table III). One possibility would be antibody-induced platelet activation with induction of a prothrombotic state in the absence of substantial platelet loss. This possibility is facilitated by the existence of at least 2 distinct interactions between anti-PF4/heparin antibodies and platelets. Platelet factor 4 that is released from platelet α granules binds to platelet surface glycosaminoglycans. These complexes are targeted by anti-PF4/heparin antibodies[20] to produce platelet activation. Interestingly, heparin is not necessary for binding HIT antibodies to

Table III. ELISA-positive nonthrombocytopenic patients: potential mechanisms underlying cardiovascular risk

1. Undiagnosed HIT (relative thrombocytopenia)
2. Platelet activation in absence of thrombocytopenia
   a. Differential effects of $F(ab)_2$ versus Fc-platelet interactions
   b. Leukocyte-platelet and endothelial-platelet aggregates
3. Nonplatelet Ab targets:
   a. Endothelial activation
   b. Monocyte-derived tissue factor generation
   c. Leukocyte degranulation with myeloperoxidase release
   d. NAP-2 and IL-8
4. Facilitation of a systemic inflammatory state

NAP-2, Neutrophil-activating peptide 2.

platelet surface-bound PF4,[20,21] providing a possible mechanism for thrombotic risk extending beyond the duration of heparin exposure. Thus, anti-PF4/heparin antibodies can bind to platelets via an interaction between the Fc fragment and platelet Fc γ RIIA or by the $F(ab)_2$ region interacting with surface-bound PF4. These 2 types of antibody-platelet interactions might lead to distinct profiles of platelet activation occurring with or without concomitant thrombocytopenia.

It is also possible that anti-PF4/heparin antibodies increase adverse events by mechanisms completely independent of platelet activation. It is known that the $F(ab)_2$ fragment (but not the Fc fragment) of IgG anti-PF4/heparin antibodies bind to and activate microvascular endothelial cells.[22] Anti-PF4/heparin $F(ab)_2$ fragments augment release of interleukin (IL) 6, vWF, and soluble thrombomodulin.[22] Furthermore, microvascular endothelial cells exposed to anti-PF4/heparin antibodies increased expression of adhesion molecules (P-selectin, E-selectin, and vascular cellular adhesion molecule 1).[22] The interaction of antibody with endothelial cells depended on the presence of either platelets[23] or purified PF4 and could be abolished by degrading cell-surface glycosaminoglycans with heparinase. These experiments were performed with IgG -derived $F(ab)_2$. The clinical evidence that IgA and IgM antibodies contribute to HIT-related thrombosis remains controversial.[6,7,24,25] Nevertheless, although IgA and IgM do not ligate Fc γ RIIA, they bind to the PF4/heparin complex, suggesting that involvement of these immunoglobulin classes remains plausible.

The induction of tissue factor expression by monocytes[26] represents another prothrombotic effect of anti-PF4/heparin antibodies. Pouplard et al[26] reported that purified HIT IgG, in the presence of PF4, induced tissue factor expression by monocytes.[26] Heparin-induced thrombocytopenia antibodies also have been demonstrated to induce platelet-leukocyte aggregates in a heparin-dependent interaction.[27] Platelet-leukocyte aggregation is mediated by platelet P-selectin interacting with polymorphonuclear leukocytes and monocytes.[28]

Autoantibodies to PF4/heparin may elicit an inflammatory response that is the proximate cause for recurrent thrombotic events. Alternatively, anti-PF4/heparin antibodies are not direct mediators of the inflammatory process but instead act as markers for a generally heightened inflammatory response. Evidence exists to support this hypothesis, as higher levels of C-reactive protein, myeloperoxidase, and soluble adhesion molecules have been demonstrated in patients with heparin antibodies.[28,29] It is also conceivable that antibodies to other protein targets produced concurrently with anti-PF4/heparin antibodies might contribute to risk for subsequent thrombotic events. Platelet factor 4 is a member of the CXC family of chemokines.[30] Antibodies to other family members including IL-8 and neutrophil-activating peptide 2 have been described,[31] although it is not currently apparent how these antibodies might promote thrombosis. It is interesting to note that anti-PF4/heparin antibodies have been identified in patients with ACS before heparin exposure, suggesting an underlying autoimmune predisposition.[32] Patients predisposed to develop anti-PF4/heparin antibodies may be at risk for generation of other autoantibodies or a heightened inflammatory state—conditions more directly linked to thrombotic propensity.

As noted, some studies have found that heparin antibodies increase the occurrence of thrombotic events, whereas others have failed to document this association. In general, studies with lower-risk patient populations (eg, elective surgery or prophylactic anticoagulation) have not demonstrated an increased risk from heparin/PF4 antibodies. It has been demonstrated in a mouse model[33] that host-specific factors, such as hypercholesterolemia-induced platelet and endothelial activation, influence the occurrence of thrombotic events in the presence of anti-PF4/heparin antibodies.[33] Accordingly, antibody-positive patients with existing arterial and venous thrombosis may be more likely to have recurrent thrombotic events than those who are being treated to prevent an initial event. These considerations may explain the variability that has been observed in studies exploring the association between anti-PF4/heparin antibodies and adverse events.

Strategy for evaluating the patient with heparin antibody and normal platelet count

Although clinical studies do not uniformly demonstrate increased risk from anti-PF4/ heparin antibodies, the association in certain high-risk clinical scenarios raises concern. Prospective application of this knowledge to patient care must weigh enhanced sensitivity for detecting patients at risk versus increased costs for antibody testing. Ultimately, patient populations that

Figure 1

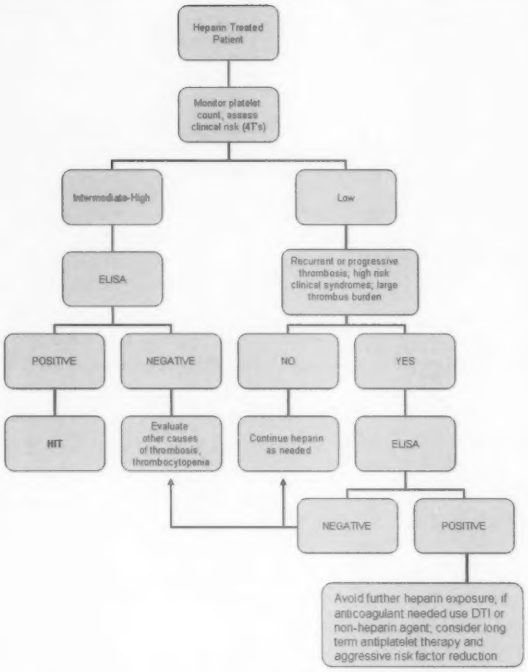
4T's	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall > 50% and platelet nadir ≥ 20	Platelet count fall 30-50% or platelet nadir 10-19	Platelet count fall < 30% or platelet nadir <10
Timing of platelet count fall	Clear onset between days 5-10 or platelet fall ≤ 1 day (prior heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear (e.g. missing platelet counts), onset after day 10, or fall ≤ 1 day (prior heparin exposure 30-100 days ago)	Platelet count fall < 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed), skin necrosis, acute systemic reaction (post intravenous unfractionated heparin (UFH) bolus	Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, suspected thrombosis (not proven)	None
Other causes for thrombocytopenia	Non apparent	Possible	Definite

Low probability ≤ 3 points; intermediate 4-5 points; high 6-8 points

Modified from Table 1, page 760 of Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4:759-765. Permission granted for reprint.

The 4T's scoring system for HIT.

Figure 2



Proposed ELISA testing strategy for heparin treated patients.

should be tested for anti-PF4/heparin antibodies and management of those with positive tests must be directed by prospective clinical trials. Specifically, it is unknown whether selective use of heparin-free anticoagulants in antibody-positive patients will improve clinical outcomes. In the absence of definitive clinical data, we do not advocate uniform antibody testing in all patients receiving heparin, as this practice would be unlikely to prove efficacious from a cost/benefit standpoint. Rather, we favor a more conservative approach that broadens application of the "4 Ts" score, a proposed diagnostic tool to predict an individual patient's likelihood for diagnosis of HIT (Figure 1).

The 4 Ts scoring system relies on presence of thrombocytopenia, with the magnitude of decline in platelet concentration and timing of thrombocytopenia relative to heparin exposure being 2 major determinants of diagnostic score.[34] In this system, a high-risk score will not occur in the absence of at least a 30% decline in platelet concentration below baseline. In clinical trials at 2 centers (Ontario, Canada, and Greifswald, Germany), a low clinical T score predicted a low likelihood of testing positive for anti-PF4/heparin antibodies by either functional assay (serotonin release assay, heparin-induced platelet aggregation) or IgG-based ELISA.[34] Altogether, 7.3% and 15.6% of patients with low clinical scores at the 2 clinical sites tested positive by ELISA. Two of the patients with a low clinical T score and positive ELISA experienced a new thrombotic complication, but these were attributed to a preexisting consumptive coagulopathy. Accordingly, the authors advocated limiting serological tests to patients with intermediate or high pretest clinical scores for HIT. The authors suggested that a patient with a low pretest probability for HIT might fare better by continued treatment with heparin rather than substitution of a nonheparin anticoagulant—particularly in the absence of preexisting thrombosis.[34]

Although a low pretest score (4 Ts) correlates with a low rate of clinical HIT, an antibody prevalence of 16% is not negligible, especially given the widespread prevalence of heparin exposure in hospitalized patients. In certain clinical situations, antibody prevalence is exceptionally high. After cardiovascular surgery, for example, seroconversion rates exceeding 50% have been documented in several studies.[35-39] Furthermore, correct determination of etiology underlying thrombocytopenia or a thrombotic event often proves challenging. After cardiac surgery, decrements in platelet count may be attributable to hemodilution, platelet consumption during cardiopulmonary bypass, drug-mediated effects, or infection. Accurate analysis of platelet count trends may be complicated by platelet transfusions. Furthermore, thrombotic events initiated or exacerbated by anti-PF4/heparin antibodies might be attributed mistakenly to the primary clinical event or surgery. For example, acute occlusion of a saphenous vein graft in a coronary artery bypass graft surgical patient with anti-

PF4/heparin antibodies easily might be attributed to a failure of surgical technique rather than an anti-PF4/heparin antibody–mediated event.

Considering evidence that anti-PF4/heparin antibodies can initiate thrombosis in the absence of thrombocytopenia, and given the ambiguities in estimating platelet concentration trends and determining underlying origins of thrombosis, we recommend an approach that broadens antibody testing to include certain "low-risk" patients. Our approach to ELISA testing in heparin-treated patients is outlined in Figure 2. All intermediate and high-probability (4 Ts) patients should undergo ELISA testing. If the test is positive, these patients should be treated for HIT; if the ELISA is negative, other potential causes for thrombocytopenia and/or thrombosis should be explored. In the low probability group, we advocate ELISA testing for patients with recurrence or progression of thrombosis during heparin therapy and for clinical scenarios at increased risk for recurrent thrombosis. Patients with conditions that are associated with prolonged or repeated exposure to heparin also would be candidates for ELISA testing. Finally, the presence of a large ongoing thrombotic burden would pose a host-specific factor that could predispose to recurrent events in the presence of heparin/PF4 antibodies.

In 1994, Kelton and Warkentin[40] conceptualized a graphic "iceberg" model to describe the association between anti-PF4/heparin antibodies, thrombocytopenia, and HIT. The largest component of the iceberg, composed of patients with positive serologies for HIT in the absence of thrombocytopenia or other clinical signs, appeared at the base—unseen, below the surface. Recent investigations, reviewed within this manuscript, suggest that just as the unseen portion of an iceberg poses a greater risk than the more obvious visible portion, anti-PF4/ heparin antibodies in asymptomatic patients may pose a previously unrecognized risk.[41] Anti-PF4/heparin antibodies appear, in certain subsets of patients, to pose an independent risk for thrombotic events—regardless of the presence of thrombocytopenia. In the future, more widespread testing for anti-PF4/heparin antibodies may be advisable. However, given that current publications do not uniformly report a direct association between anti-PF4/heparin antibodies and adverse outcomes, we currently advocate a more focused approach with laboratory screening of low-risk patient populations only in specific clinical settings.

In the future, administration of unfractionated heparin and the inherent risk of anti-PF4/heparin antibody generation may decline. Low-molecular-weight heparins (LMWHs) are gaining favor for treatment of ACS as well as venous thromboembolism. The OASIS trials[42,43] demonstrated efficacy of fondaparinux for patients with either non-ST or ST-elevation myocardial infarctions. Both LMWH and fondaparinux carry significantly lower risk for anti-PF4/heparin generation and HIT than unfractionated heparin. Finally, bivalirudin and other direct thrombin inhibitors offer alternatives to heparin during PCIs[44] (and other conditions requiring anticoagulation) with no risk for inducing anti-PF4/heparin antibodies and/or HIT.

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Human epicardial adipose tissue: A review

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We discuss the anatomy, physiology, and pathophysiology of epicardial adipose tissue and its relationship to coronary atherosclerosis. Epicardial fat stores triglyceride to supply free fatty acids for myocardial energy production and produces adipokines. It shares a common embryological origin with mesenteric and omental fat. Like visceral abdominal fat, epicardial fat thickness, measured by echocardiography, is increased in obesity. Epicardial fat could influence coronary atherogenesis and myocardial function because there is no fibrous fascial layer to impede diffusion of free fatty acids and adipokines between it and the underlying vessel wall as well as the myocardium. Segments of coronary arteries lacking epicardial fat or separated from it by a bridge of myocardial tissue are protected against the development of atherosclerosis in those segments. However, when epicardial fat is totally absent in congenital generalized lipodystrophy, coronary atherosclerosis can still occur. Macrophages are more numerous and densely packed in the periadventitial fat of human atherosclerotic coronary arteries with lipid cores than in that of fibrocalcific or nonatherosclerotic coronary arteries. In obese patients with multiple cardiovascular risk factors, epicardial fat around atheromatous coronaries secretes several proinflammatory cytokines and is infiltrated by macrophages, lymphocytes, and basophils. Epicardial adipokine expression in obesity without coronary atherosclerosis has not been determined. In nonobese patients, epicardial fat around atheromatous coronary arteries expresses proinflammatory cytokines but produces either less adiponectin, a vasoprotective adipokine, than fat around nonatheromatous coronaries or a similar amount compared with thoracic subcutaneous fat. Further studies should be done to test the hypothesis that adipokines produced by and released from human epicardial adipose tissue might contribute locally to the pathogenesis of coronary atherosclerosis. (Am Heart J 2007;153:907-17.)

Human epicardial adipose tissue (EAT) is a visceral thoracic fat because of its apposition to the heart, to a hollow muscular organ, or to the viscus. It has not been studied as thoroughly[1] as visceral abdominal adipose tissue (VAT) and subcutaneous abdominal adipose tissue (SCAT).[2] Like other white adipose tissue loci,[3-6] EAT might function as a lipid-storing depot, as an endocrine organ secreting hormones, and as an inflammatory tissue secreting cytokines and chemokines. Under these conditions, its proximity to the adventitia of the coronary arteries (Figure 1) and the underlying myocardium suggests the possibility that it could play a role in the pathogenesis of coronary atherosclerosis (CAD), itself a chronic inflammatory disease,[1] and cardiomyopathy (CMO). The obesity epidemic in children[7] and adults has drawn attention to VAT and the metabolic syndrome[8] as risk factors for cardiovascular disease (CVD) and type 2 diabetes mellitus (DM)[9,10] and poses whether obesity per se could affect EAT and its adipokine content.

We discuss the anatomy and physiology of human EAT, the pathophysiology of white adipose tissue in obesity compared to the nonobese state, the pathophysiology of EAT, and the putative role of EAT in the pathogenesis of CAD and CMO.

Anatomy and physiology of EAT

The epicardium or visceral layer of the pericardium is a population of mesothelial cells that migrate onto the surface of the heart from the area of the septum transversum (the embryological source of the diaphragm). Epicardial, mesenteric, and omental fat all share the same origin from the splanchnopleuric mesoderm associated with the gut.[11] In the normal adult, epicardial fat is concentrated in the atrioventricular (AV) and interventricular (IV) grooves and along the major branches of the coronary arteries, and, to a lesser extent, around the atria, over the free wall of the right ventricle (RV) and over the apex of the left ventricle (LV).[12,13] Pericardial fat (pericardial adipose tissue [PAT]) is defined as epicardial fat in all these possible locations plus paracardial fat.[14] Paracardial fat is situated on the external surface of the parietal pericardium within the mediastinum and has alternatively been termed mediastinal fat.[15]

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Figure 1

Histology of the right coronary artery and periadventitial epicardial fat. This high power (×100 magnification) hematoxylin and eosin stain of a transverse autopsy section of the right coronary artery from a patient with hypertensive heart disease shows the layers of the artery wall, the tissue structures in epicardial fat, and the close contact of epicardial adipocytes with the adventitia.

Paracardial fat originates from the primitive thoracic mesenchyme, which splits to form the parietal (fibrous) pericardium and the outer thoracic wall.[16] Epicardial adipose tissue is supplied by branches of the coronary arteries, whereas paracardial fat is supplied from different sources including the pericardiacophrenic artery, a branch of the internal mammary.[17]

Lipolysis and lipogenesis have not been measured directly in human epicardial fat. Based on approximately 2-fold higher rates of lipolysis and lipogenesis in guinea-pig epicardial fat than other fat depots, Marchington et al[18,19] proposed that EAT serves to capture and store intravascular free fatty acid (FFA) to protect cardiomyocytes from exposure to excessive coronary arterial FFA concentrations during increased energy intake and, at other times, to release FFA as an immediate ATP source for the myocardium during periods of need. Epicardial fat and the myocardium are contiguous. Islands of mature adipocytes are more frequent within the subepicardial myocardium of the RV than the LV[13] and may act as more readily available, direct sources of FFA for cardiomyocytes. The thickness of the wall of the right atrium is about 2 mm; the left atrium, 3 to 5 mm; the RV, 3 to 5 mm; and the LV, 13 to 15 mm.[20] Possibly, FFAs could diffuse bidirectionally in interstitial fluid across concentration gradients from epicardial fat into the atrial and RV walls where EAT predominates and vice versa, but this process in the LV wall can be questioned because the diffusion distance is much longer.

In normal humans, systemic fat stores are the principal source of FFAs for the heart.[21] The myocardium extracts and metabolizes FFAs from coronary arterial blood. Free fatty acid kinetic studies show that under normal basal conditions, endogenous FFAs are released into the coronary veins and then into the coronary venous sinus.[21,22] The source for this FFA release is thought to be EAT lipolysis,[22] since other possibilities such as hydrolysis of intracardiomyocyte triglyceride or hydrolysis of circulating very-low-density-lipoprotein-triglyceride in coronary blood[21] seem unlikely. The reason for FFA efflux into coronary venous blood is unclear. It might represent an "overflow" of FFAs not used by the myocardium. Alternatively, it might be a direct source of FFAs for the pulmonary arterial circulation, since vasoactive prostanoids are generated by the pulmonary arterial endothelium from FFA precursors.[23] The fact that coronary sinus FFA appearance accounts for a minor fraction of systemic FFA flux[22] supports the hypothesis that EAT functions as a local myocardium-specific triglyceride depot. Epicardial adipose tissue might secrete vasoactive products that regulate coronary arterial tone. For example, adipocyte-derived relaxing factor, a protein recently isolated from normal rodent aortic and mesenteric arterial periadventitial fat,[24] stimulates arterial vasodilation independently of nitric oxide by diffusing into the media of the coronary wall, normally 0.55 to 1.0 mm thick.[25] It is different from leptin[24] and adiponectin.[26]

Quantitation of EAT

Autopsy

Corradi et al[27] dissected epicardial fat from the underlying myocardium in a series of 117 patients and found that it accounted for approximately 15% (mean, 54 ± 23 g [±SD]) of a normal heart weight (365 ± 49 g). They also found a direct correlation between LV and RV mass and corresponding epicardial fat mass. In a later study, the same authors confirmed the direct correlation ($r = 0.755$, $P = .01$) between EAT mass and myocardial ventricular mass measured by echocardiography in 60 subjects with no known cardiac disease.[28] In an unselected group of 200 patients dying from a variety of diseases including carcinoma and arteriosclerosis studied by Schjebal,[29] epicardial fat thickness over the RV wall varied from zero along the fat-free diaphragmatic region to 13.6 mm along the sharp ventrolateral edge close to the base, the maximal point of thickness. In that report, EAT thickness correlated directly with subcutaneous fat thickness and was 1.65-fold greater in women in each of these locations. Duflou et al[30] measured EAT thickness in 3 selected age-matched groups of subjects: group 1—22 massively obese adults (mean weight, 175 ± 68 kg; body mass index [BMI], 57 ± 12.8 kg/m^2 [± SD], currently classified as morbid obesity) who died suddenly; group 2—6 massively obese adults (weight, 131 ± 25 kg;

Table I. Correlations between epicardial and pericardial versus visceral abdominal and SCATs

Study (n)	BMI (kg/m2)	Radiological method	Correlations	Reference
Italian				31
Men and women (72)	34.0 ± 14.5 (SD)	ECHO	EAT vs VAT*: $r = 0.84$, $P = .001$ EAT vs SCAT*: NS	
Italian				32
Women lean (15)	22.6 ± 1.7(SD)	ECHO	EAT vs VAT†: $r = 0.80$, $P < .0001$	
Women obese (27)	43.5 ± 4.8		EAT vs VAT/SCAT†: $r = 0.74$, $P = .0001$	
Italian				15
Men (23)	27.7 ± 0.6(SEM)	MRI	EAT vs VAT: NS PAT‡ vs VAT: $r = 0.66$, $P < .0006$ PAT‡ vs SCAT: NS	
American				14
Men and women (80)	31.9 ± 7.3(SD)	CT	PAT§ vs VAT: $r = 0.81$, $P < .0001$ PAT§ vs SCAT: not reported	
Japanese				17
Men nonobese (181)	22.7 ± 2.0(SD)	CT	PAT§ vs VAT: $r = 0.791$, $P < .001$ PAT§ vs SCAT: $r = 0.470$, $P < .001$	
Men obese (64)	27.6 ± 2.3(SD)		PAT§ vs VAT: $r = 0.692$, $P < .001$ PAT§ vs SCAT: $r = 0.410$, $P < .001$	

NS, No statistically significant correlation.
*Measured using MRI.
†Measured using CT.
‡Measured as mediastinal (paracardial) adipose tissue.
§Measured as paracardial plus epicardial adipose tissue.

BMI, 45 ± 3.4 kg/m^2) who died of unnatural causes; group 3—11 nonobese adults (weight, 84 ± 24 kg; BMI, 27 ± 3.9 kg/m^2, currently classified as overweight) who died of trauma. Epicardial fat was measured in the AV grooves at the right and left lateral borders of the heart and on the epicardial surface of the IV septum, 2 cm distal to the origin of the left anterior descending coronary artery. The following is an epicardial fat index, calculated as the mean of the 3 epicardial fat measurements taken in each case: group 1, 11 ± 3.2 mm (±SD); group 2, 11 ± 2.0 mm; group 3, 11 ± 2.0 mm. Thus, in this autopsy series, mean EAT thickness around the coronary arteries did not differ over the BMI range of 27 to 57 kg/m^2. Their results cannot be directly compared with those of Schjebal's[29] because their measurements were made in the AV grooves and the anterior IV septum rather than the RV free wall, as well as in patients selected according to body weight and mode of death as opposed to a randomly selected group of autopsy patients.

Radiology

In healthy people (n = 72) with BMI 22 to 47 kg/m^2, Iacobellis et al[31] used ECHO to measure epicardial fat and found that the maximal thickness at any site over the free wall of the RV varied between 1.8 and 16.5 mm. These authors emphasized that they chose to measure epicardial fat on the RV for 2 reasons: (i) this point is recognized as the highest absolute epicardial fat layer thickness, and (ii) their use of parasternal long- and short-axis views allow the most accurate measurement of EAT on the RV, with optimal cursor beam orientation in each view. Also using ECHO, Malvazos et al[32] reported mean EAT values on the free wall of the RV of 1.3 ± 0.2 mm (SD) in 15 healthy lean (BMI, 22 ± 1.7 kg/m^2) and 6.5 ± 0.8 mm in 27 healthy obese (BMI, 43 ± 4.8 kg/m^2) women ($P < .0001$). Abbara et al[33] point out that ECHO cannot give an adequate window of all cardiac segments and is highly dependent on acoustic windows, which are often inadequate for subtle assessments in obese patients, resulting in an insufficient examination.[34] Abbara et al[33] measured EAT using 16-slice scanner, multidetector computerized tomography (MDCT) to assess CAD imaging in 59 adults (BMI not reported) in a mapping study designed to facilitate transepicardial arrhythmia ablation. The MDCT has advantages of submillimeter collimation, high temporal and spatial resolution, and 3-dimensional views of the heart and its epicardial surface. The following are the mean EAT thickness at different sites in descending order of magnitude: right AV groove, 14.8 mm; left AV groove, 12.7 mm; superior IV groove, 11.2 mm; inferior IV groove, 9.2 mm; acute margin, 9.2 mm; anterior IV groove, 7.7 mm; RV anterior free wall inferior, 6.8 mm; RV anterior free wall superior, 6.5 mm; RV superior wall, 5.6 mm; RV apex, 4.8 mm; LV apex, 2.8 mm; RV diaphragmatic wall, 1.4 mm; and LV superior lateral wall, 1.0 mm. Mean EAT thickness for all patients was 5.3 ± 1.6 mm (SD). Total EAT content was on average 22% greater for patients more than 65 years of age and 17% greater in women in agreement with an autopsy report.[29] Therefore, in this cohort, the thickest part of EAT was in its grooved and not, as some authors[29,31] suggest, in the nongrooved segments that include the free wall of the RV.

Magnetic resonance imaging (MRI) also has limitations for EAT determination in terms of its lower spatial resolution, specifically in the through plane dimension (z-dimension).[33] Nevertheless, it is considered the "gold standard" for visceral fat measurement.[35] The MRI and ECHO measurements of EAT made over the free wall of the RV correlate well ($r = 0.91$, $P = .001$).[31]

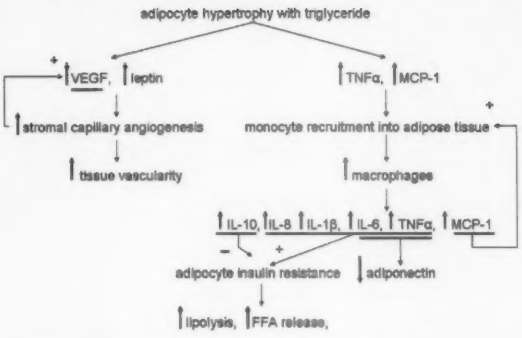
Correlations between EAT and PAT versus VAT and SCAT determined radiologically are shown in Table I. In 72 healthy adults with BMI 22 to 47 kg/m^2, EAT thickness determined by ECHO correlated significantly with VAT measured by MRI ($r = 0.84$, $P = .001$) and with waist circumference ($r = 0.845$, $P = .01$).[31] The association was less with BMI ($P = .05$), and there was none with total fat mass ($P = .1$). Malavazos et al[32] confirmed that EAT thickness by ECHO over the free wall of the RV was significantly related to VAT ($r = 0.8$, $P < .0001$). Sironi et al[15] used MRI to measure EAT, VAT, and PAT (mediastinal) fat in 13 hypertensive insulin-resistant overweight men (BMI, 28 $\pm$ 0.7 kg/m^2 [SE]) and 26 normotensive insulin-sensitive age- and BMI-matched (27 $\pm$ 0.5 kg/m^2) controls. Unlike the ECHO study discussed above,[31] there was no correlation between EAT and VAT areas in both groups. The hypertensive group had significantly more PAT (45 $\pm$ 5 vs 28 $\pm$ 3 cm^2; $P = .005$), but there was no difference in EAT area. There was a direct relationship between PAT and VAT for the combined groups (n = 23; $r = 0.66$; $P < .0006$). In a cohort of 69 patients with DM and 11 non-DM siblings, PAT volume determined by computed tomography (CT) correlated with VAT volume determined by CT ($r = 0.81$) compared to waist circumference ($r = 0.63$) and BMI ($r = 0.47$),[14] all being significant ($P < .0001$).[14] Epicardial adipose tissue volume alone was not determined. Another striking finding was the wide variability of pericardial fat volumes ranging from 84 to 899 mL with a mean of 320 mL compared to mean VAT of 3046 mL. In a Japanese study,[17] PAT measured by CT in 181 nonobese men with BMI 22.7 $\pm$ 2.0 kg/m^2 (SD) correlated with both VAT ($r = 0.791$, $P < .001$) and with SCAT ($r = 0.470$, $P < .001$), as did PAT with VAT ($r = 0.692$, $P < .001$) and with SCAT ($r = 0.410$, $P < .001$) in 64 obese men with BMI of 27.6 $\pm$ 2.39 kg/m^2.[17] In summary, in 2 CT studies, PAT correlated with VAT, but EAT per se was not measured. In 2 studies, EAT determined by ECHO correlated with VAT by MRI and CT. In one study, EAT by MRI did not correlate with VAT, possibly because of differences in the selection of subjects.

Pathophysiology of adipose tissue and adipokines in obesity

The pathophysiology of adipokine expression and secretion in VAT and SCAT needs to be reviewed to provide a conceptual basis for understanding adipokine pathophysiology. In contrast to the lack of studies comparing EAT in healthy nonobese and obese humans, the expression and secretion of adipokines in VAT and SCAT have been well documented in biopsies taken from lean healthy patients at elective intra-abdominal surgery as compared with biopsies from obese healthy patients undergoing bariatric procedures.[36-39] In other studies, omental VAT and SCAT in obesity[3,40,41] or SCAT from lean and obese subjects[42,43] or SCAT before and after weight loss[42,44] have been determined. Collectively, the data indicate that obese VAT and SCAT contain more macrophages, tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-8, IL-10, resistin, monocyte chemoattractive protein-1 (MCP-1), plasminogen activator inhibitor-1, (PAI-1), angiotensinogen (AGT), vascular endothelial growth factor (VEGF), transforming growth factor β1, and less adiponectin and leptin than lean VAT and SCAT.

Definitions of adipocytokine and adipokine vary.[3-6] We define an adipokine as a hormone, cytokine, or chemokine secreted from intact adipose tissue, which is composed of a mixture of cells including adipocytes and preadipocytes, macrophages, lymphoctes, endothelial cells, mast cells, basophils, and fibroblasts.[44] A commonly used term for the nonadipocytes of adipose tissue is the stromal-vascular matrix (SVM).[44] IL-1β, IL-6, IL-8, IL-10, TNF-α as well as resistin and VEGF are released primarily by the nonadipocytes (SVM), whereas the

Figure 2



Pathophysiology and adipokine signaling in obese adipose tissue. Adipocytes hypertrophy with triglyceride when energy intake exceeds expenditure resulting in obesity. This triggers a cellular and molecular inflammatory cascade with positive feedback loops involving VEGF and MCP-1. The consequences are increased adipose tissue vascularity along with enhanced accumulation of macrophages and release of cytokines by the non–fat cells in adipose tissue, local insulin resistance with accelerated lipolysis and FFA release, and decreased adiponectin production and increased leptin release by adipocytes. Plus sign indicates stimulation; negative sign, inhibition.

chemokines, MCP-1, and macrophage migration inhibitory factor,[45] as well as nerve growth factor and serum amyloid A1 and 2 proteins are produced to a somewhat greater extent by human adipocytes.[44] However, it should be emphasized that most inflammatory cytokines released by obese human VAT and SCAT are derived from the nonadipocytes, except for leptin and adiponectin.[3,44]

The primary physiological role of adipocytes in adipose tissue is as a depot in which to store fat as energy when energy intake exceeds energy expenditure and to release FFAs on demand.[4] As an additional function, when adipocytes in VAT and SCAT hypertrophy with triglyceride during obesity, they secrete TNF-α and MCP-1, and the macrophage number increases within the 2 fat depots that, as a result, transform into inflammatory tissues[46] (Figure 2). Circulating lymphocytes, and monocytes attracted by MCP-1 secreted by these expanding adipocytes,[43,47] diapedese across the endothelium of adipose tissue capillaries into the SVM. Monocyte chemoattractive protein-1 is essential for promoting monocyte entry into the SVM as shown by MCP-1[48] and MCP-1 receptor (CCR2)[49] knockouts that negate monocyte diapedesis. Recruited monocyte-transformed macrophages in the SVM are termed activated M1-polarized macrophages and express CCR2 ($CCR2^+$).[50] These macrophages secrete MCP-1 to amplify monocyte recruitment, and together with activated endothelium, also produce proinflammatory TNF-α, IL-1β, IL-6, and IL-8,[46,51] which, with adipocyte-derived TNF-α autocrine feedback, inhibit insulin signaling in adipocytes via paracrine cross-talk.[52] The result is adipocyte insulin resistance and lipolysis of stored triglyceride into FFAs.[36,52,53] In response, resident $CCR2^-$ alternatively activated M2-polarized macrophages increase the release of the anti-inflammatory cytokine IL-10 to protect adipocytes from these inflammatory factors.[50] Both TNF-α and IL-6 with its soluble receptor inhibit adiponectin production.[54] The endothelium produces VEGF,[55] and the adipocytes produce leptin and VEGF, which stimulate angiogenesis to increase adipose tissue vascularity parri passu with adipocyte expansion when it occurs.[46,56] Free fatty acids released from VAT into the hepatic portal vein are substrates for hepatic synthesis of atherogenic apoprotein B-containing VLDL-trigylceride particles that are subsequently released into the peripheral circulation.[57]

Pathophysiology of EAT

Epicardial fat in obesity

In their 1933 report on adiposity of the heart, Smith and Willius[58] performed autopsies on 136 obese patients (mean 43% above ideal body weight; range, 13%-103%). They noted that "in most instances, a definite relationship between the excess of epicardial fat and the degree of general obesity occurred." This observation was based on increased heart weight and not on dissected epicardial fat mass. As epicardial fat increases, it extends over the anterior surface of the heart, more over the RV than the LV and, lastly, over the LV midway between the apex and base.[13] The coronary arteries become encased by or displaced in front of the enlarged epicardial fat layer or lie between it and the myocardium.[58] The amount of fat is variable and in extreme obesity can cover the heart completely in fat 2 cm thick or more ("cor adipe plane tectum"). Fat also penetrates from the subepicardial connective tissue into the connective tissue lying between the muscle bundles and muscle fibers, defined as adiposity of the heart.[58]

Adiposity of the heart must be distinguished from obesity-specific lipotoxic cardiomyopathy (LCMO),[59] in which excessive fat accumulates inside cardiac muscle and causes LV remodeling and CMO, independent of other causes of myocardial disease in obesity such as hypertension and CAD.[60] The LCMO develops after normal sites of fat storage in subcutaneous adipose tissues, and VAT are filled to capacity in obesity and release FFAs into blood. Excess circulating FFAs are removed and converted into triglyceride by cardiomyocytes as well as other cells in which small quantities of fat are normally present, such as hepatocytes, skeletal myocytes, and pancreatic islet β-cells. The fat accumulates intracellularly as droplets in the cytosol in these "ectopic" sites, resulting, respectively, in myocardial steatosis and a specific dilated CMO, nonalchoholic steatohepatitis and cirrhosis, and DM.[60] At the molecular level, the current hypothesis is that LCMO is not due to triglyceride accumulation alone but is the consequence of accumulating by-products of lipid metabolism such as ceramide or other fatty acid derivatives that interfere with intracellular signaling pathways through phosphatidylinositol 3-kinase and nuclear factor κB.[59] Ceramide is a sphingosine signaling molecule that increases inducible nitric oxide synthase activity and intracellular nitric oxide leading to cardiomyocyte apoptosis.[61] Putatively, FFAs released from hypertrophied adipocytes in EAT could diffuse directly into the myocardium, together with myocardial uptake of plasma FFAs,[22] exacerbating myocardial steatosis, and lipotoxicity. Structurally and functionally, the consequences of intracardiac lipotoxicity and extracardiac adiposity include increased heart weight and mechanical pumping effort,[62] LV hypertrophy, LV diastolic dysfunction, cardiac failure, electrocardiographic abnormalities, and increased arrhythmogenicity.[63]

The role of EAT in CAD

Obesity is an independent risk factor for CVD.[63] Epicardial adipose tissue thickness, determined by ECHO over the free wall of the RV, correlates with VAT (a CVD risk factor per se), other correlates of CVD such as waist

Table II. The relationship between EAT and CAD

Study (reference)	Principle findings	Limitations
Hypercholesterolemic white rabbits[68]	Atherosclerotic lesions were absent in intramyocardial but present in intraepicardial portions of the left anterior descending coronary artery surrounded by fat	Differences may have been due to hemodynamic protective effects on transendothelial lipid permeability but a role for adipokines was plausible
Human myocardial bridge[69]	Atherosclerotic intimal lesions were absent in the part of left anterior descending artery covered by myocardium while running through epicardial fat	Protection of intima may have been due to hemodynamic forces during bridge contraction, but a role for adipokines was feasible
Human anomalous coronary artery origin from the sinus of Valsalva[70,71]	Atherosclerotic intimal lesions were absent in the proximal coronary trunk lying in the subadventitial wall of aorta, despite distal CAD and multiple risk factors in some cases	Intima of intra-aortic coronary segment might have been protected by hemodynamics during aortic contraction in diastole
Congenital generalized lipodystrophy[72,73]	Epicardial, visceral, and subcutaneous abdominal fat were absent, yet CAD was found at autopsy	It was unknown if the extent of surface lesions was worse or better than age- or sex-matched controls
Balloon overstretch injury of porcine coronary arteries[74]	Macrophages and neutrophils occurred in and chemokines/cytokines were expressed from epicardial fat several millimeters from the site of adventitial injury	The pathophysiologic relevance to lipoprotein-induced intima-media injury was not clear
Human CAD/CABG surgery[75]	More mRNA for and secretion of MCP-1, IL-1β, IL-6, and TNF-α, and more chronic inflammatory cells were found in epicardial fat than leg subcutaneous fat	Adipokines did not correlate with extent of CAD, risk factors, and BMI, and there were no data in controls without CAD
Human CAD/CABG surgery[76]	There was less adiponectin protein in epicardial fat than in controls with valvular heart disease without CAD	No inflammatory cells were seen in CAD and control epicardial fat, and no other adipokines were measured
Human CAD/CABG surgery[77]	There was less adiponectin, IL-6, PAI-1, and leptin mRNA, and more macrophage infiltration, resistin, and AGT mRNA in epicardial than gluteal subcutaneous fat	Epicardial adipokines were compared to gluteal adipokines in separate patients rather than to epicardial adipokines in controls without CAD
Human CAD/CABG surgery Heart valve surgery[78]	There was more TNF-α but similar adiponectin, MCP-1, IL-6, resistin, and leptin mRNA in epicardial than thoracic subcutaneous fat	Epicardial and thoracic subcutaneous fat data were pooled, and it was unclear if valve patients had CAD
Human autopsy coronary arterial segments[79]	There was increased macrophage density in periadventitial fat of coronaries with lipid cores compared to coronaries with fibrocalcific plaques or no atherosclerosis	BMI was not reported
Human CAD[17]	Pericardial fat volume measured by CT correlated most strongly with severity of angiographic atherosclerotic lesions than other fat depots	Epicardial fat component of pericardial fat was not directly quantitated

circumference, diastolic blood pressure, plasma insulin, fasting plasma glucose, high-density-lipoprotein-cholesterol, low-density-lipoprotein-cholesterol, adiponectin,[31] and with insulin resistance itself measured by the insulin clamp technique.[64] Based on these 2 studies by Iacobellis et al,[31] the authors have suggested that an increased quantity of EAT in obesity may be a CVD risk predictor. For confirmation, a larger, prospective, epidemiological study, perhaps including direct measurements of pericoronary EAT thickness, should be done.

How could EAT mediate CAD? According to the response-to-retention hypothesis, atherogenesis results from the transendothelial passage (transcytosis) of cholesterol-rich atherogenic Apo-B lipoproteins (very-low-density-lipoprotein, intermediate-density-lipoprotein, and low-density-lipoprotein) from plasma into the intima, their retention in the subendothelial space (a pivotal step), their oxidative modification, the initiation and propagation of a chronic inflammatory response in the intima, media, and adventitia leading to plaque formation.[65,66] If atherosclerosis is driven primarily by luminal lipids and involves inflammation in these 3 layers of the arterial wall, could inflammation in periadventitial EAT also play a role in the pathogenesis of CAD?[1,67]

The principle findings and limitations of studies examining the relationship between EAT and CAD are presented in Table II.

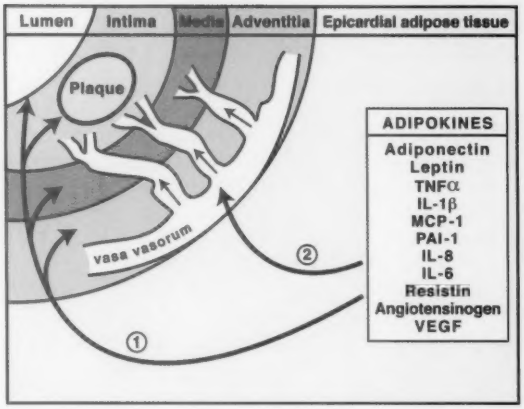
The effect of the absence of EAT on CAD. In hypercholesterolemic white rabbits, atherosclerotic lesions are absent in intramyocardial but present in intraepicardial portions of the left anterior descending coronary artery surrounded by fat.[68] In the human "myocardial bridge," atherosclerotic intimal lesions are not seen in the part of the left anterior descending coronary artery covered by myocardium, which separates the artery running through epicardial fat.[69] In anomalous origins of the coronary artery from the sinus

of Valsalva, atherosclerotic intimal lesions are not present in the proximal aberrant segment of the coronary trunk as it runs through the subadventitial layer of the aorta, even when multiple CAD risk factors are present and despite evidence of distal atherosclerosis.[70,71] Although these anatomical "experiments of nature" suggest a plausible role for adipokines in atherogenesis, an alternative explanation could be that protective hemodynamic forces during cardiac or aortic contraction reduce transendothelial lipid permeability into the intima. Autopsy proof of CAD despite total absence of EAT, VAT, and SCAT in patients with congenital generalized lipodystrophy[71,72] proves that EAT is not necessary for atherosclerosis to develop and progress but does not exclude a secondary role for it in atherogenesis. The extent of surface lesions was not quantified, which would have permitted a determination of whether the severity of arterial disease in congenital generalized lipodystrophy was worse or better than that in age- and sex-matched normal controls considering concomitant insulin-resistant DM and hyperlipidemia as CVD risk factors.

Effects of experimental coronary artery injury. In balloon overstretch injury of the media of porcine coronary arteries, macrophages, neutrophils, and adipokine expression were found in EAT several millimeters from the site of adventitial injury compared with few or none in controls,[74] suggesting a signaling system between media-adventitia and EAT. However, the pathophysiological relevance of these findings to lipoprotein-induced intimal injury is unclear.

Epicardial adipose tissue adipokines and histopathology at CABG. Tumor necrosis factor-α, MCP-I, IL-1β, and IL-6 mRNA expression and secretion, and chronic inflammatory cell infiltration with macrophages, lymphocytes, and basophils were increased in EAT versus leg subcutaneous fat from obese patients (BMI, 31 ± 1 kg/m^2 [SD]; n = 42) with multiple cardiovascular risk factors undergoing coronary artery bypass graft for critically stenotic CAD.[75] Epicardial adipose tissue inflammation did not seem to result from atherogenic inflammation in the underlying plaques (mediated by "inside-to-outside" signaling) and was not related to circulating cytokines implying that obese EAT per se might be proinflammatory. Notably, adipokine expression and secretion in a control group of patients without multiple risk factors or with noncritical CAD undergoing open-heart surgery for other indications were not studied. In addition, adipokines did not correlate with the extent of CAD, risk factors, and BMI. Adiponectin improves insulin sensitivity and has anti-inflammatory and antiatherogenic actions so that low adiponectin levels within the arterial wall, and in the circulation in metabolic syndrome and DM, may result in the loss of its potential vasoprotective effects.[80-82] Adiponectin protein levels in EAT were lower from nonobese patients (BMI, 27.4 ± 3.5 kg/m^2 [SD]) with CAD compared with controls (BMI, 25.7 ± 3.2 kg/m^2) without CAD.[76] In this study, other adipokines were not measured, and no inflammatory cells were seen in CAD and control EAT. Adiponectin mRNA in EAT from 46 nonobese patients (BMI, 27 ± 3.3 kg/m^2 [SEM]) with CAD was lower than adiponectin mRNA in omental, SCAT, and gluteal fat from 30 nonobese patients (BMI, 25.7 ± 4.7 kg/m^2) without CAD[77] confirming this trend, but the data can be questioned because of inappropriate controls. In addition, less IL-6, PAI-1, and more resistin, AGT, and macrophage CD45 mRNA was found in EAT versus gluteal fat. By contrast, in a smaller group of 15 patients (10 CABG and 5 valve replacements; BMI, 26.6 ± 1.2 kg/m^2 [SEM]), TNF-α mRNA expression in EAT was increased compared to subcutaneous thoracic fat, whereas there were no

Figure 3



Hypothetical mechanisms whereby epicardial adipokines might play a role in coronary atherogenesis. Of the adipokines identified in human EAT (inset), adiponectin and leptin are produced exclusively by adipocytes. The other adipokines are expressed in varying amounts by both adipocytes and stromal preadipocytes, macrophages, lymphocytes, fibroblasts, and endothelium. Pathway 1: Paracrine signaling. Adipokines secreted from adipocytes and stromal-vascular cells in EAT overlying the lipid core of atherosclerotic plaques diffuse in interstitial fluid across the adventitia, media, and intima and interact respectively with vasa vasora, vascular smooth muscle cells, endothelium, and cellular components of the plaque. Paracrine signaling may also occur between adipokines and FFA diffusing from epicardial fat into the underlying myocardium (not shown). Pathway 2: Vasocrine signaling. Adipokines secreted by epicardial adipocytes and stromal-vascular cells closely apposed to adventitial vasa vasorum traverse the vessel into its lumen and are transported downstream to react with cells in the media and the intima around plaques. In this model, macrophages and lymphocytes can migrate alongside the vasa vasorum through breeches in the media.[90]

differences in adiponectin, IL-6, MCP-1, resistin, and leptin mRNA in the 2 fat depots.[78] It was not clear whether the valve patients had CAD or not.

Human autopsy coronary arterial segments. CD68 macrophages were more numerous and densely packed in the periadventitial fat of atherosclerotic arteries with lipid cores than in that of fibrocalcific or nonatherosclerotic arteries.[79] Body mass index was not reported. This suggested that macrophages could enter a plaque through the adventitia or periadventitial fat even in the early stages of atherosclerosis.

Radiology. Pericardial fat area, including EAT, measured by thoracic CT correlated significantly with the extent of CAD measured angiographically in both lean (BMI, ~23) and overweight (BMI, ~28) nondiabetic Japanese men.[17] However, it is not clear to what extent EAT area per se correlated with CAD in this study.

Adipokine paracrine and vasocrine signaling

If EAT does contribute to atherogenesis, how might this come about? Figure 3 depicts hypothetical mechanisms whereby adipokines generated in EAT around atherosclerotic coronaries may access plaques in the intima. IL-1β experimentally applied to the arterial adventitia can cause inflammatory changes by diffusion into the intimal layer.[83] Thus, it is plausible that paracrine release of cytokines from periadventitial EAT could traverse the coronary wall by diffusion from "outside-to-inside" and interact with cells in each of its layers. Likewise, it has been suggested that adipokines released by macrophages and lymphocytes aggregating at the adventitia-fat interface of an atherosclerotic aortic aneurysm could diffuse into the intima-media.[84] On the other hand, during atherogenesis, cellular proliferation and plaque formation can increase the arterial wall thickness to 3 to 4 mm compared to 0.55 to 1.0 mm normally[25] so that adipokine diffusion might become less important than vascular access. In this respect, adipokines and FFAs might be released from epicardial tissue directly into vasa vasorum and be transported downstream into the arterial wall (Figure 3). This process termed "vasocrine signaling" is derived from studies by Judkin et al[85] on adventitial fat around arterioles supplying the cremaster muscle in the obese rat and may be applicable to second-order vasa vasora of similar arteriolar caliber.[86] Vasa vasora arise from bifurcation segments of the epicardial coronary arteries within the adventitia and divide into first-order parallel and second-order circumferential branches that penetrate the coronary wall to supply oxygen and nutrients to its outer two thirds, while the inner third is supplied by diffusion from the lumen.[87]

In diabetic animal models and humans with CAD, adventitial inflammation and vasa vasorum neogenesis are responsible for neovascularization of both media and intimal plaques.[88,89] The inflammatory response in the adventitia is characterized by accumulation of macrophages and B-lymphocytes.[1,90] As the vasa vasora create breeches in the media wall, they become surrounded mainly by foci of T lymphocytes and perivascular macrophages.[90] These breeches may possibly be mediated by T-helper cell-driven immune responses via interferon-γ, which inhibits vascular smooth muscle proliferation contributing to medial disruption. Vasa vasorum neogenesis is mediated by VEGF secreted by activated T lymphocytes in the intima-media,[90] but conceivably also by epicardial adipocytes, because adipocytes harvested from human donor EAT secrete VEGF and induce angiogenesis of coronary artery endothelial cells in vitro.[56] Virmani et al[90] have emphasized the critical role of vasa vasorum neovascularization in plaque hemorrhage, stability, and rupture.

Areas of future research for EAT

Current evidence implies that EAT is a contributor to the progression of CAD rather than an "innocent bystander" (an epiphenomen)[1] or an associated marker. More is needed to support this hypothesis.

Histopathology. Macrophages in plaques and adipose tissue are heterogeneous,[50,91] and subsets possessing distinct surface antigens or receptors specific for EAT and intima macrophages[92,93] may be identified and used to track the intramural movement of these cells bidirectionally. In addition, macrophage density should be measured in autopsy specimens from obese and lean patients without CAD. Superparamagnetic iron oxide nanoparticles, phagacytosed by macrophages, might be used as a contrast agent to enhance the spatial resolution of MRI for delineating active plaques in coronary arteries and inflammatory activity in EAT.[82]

Animal studies. Experiments should be performed in animals with normally discernible EAT such as rabbits,[66] pigs,[86] or monkeys[94] with high fat- or cholesterol-induced hyperlipidemia and atherosclerosis, rather than rodents that normally have little or no EAT,[18] to examine the relationship of coronary atherogenesis to adipokine expression in EAT. Because adventitial vasa vasorum angiogenesis precedes vascular lesion formation,[86] the initial molecular signals responsible for adventitial angiogenesis could arise, at least partly, from secretion of VEGF and leptin by hypertrophied adipocytes or other cell components present in EAT (Figure 2).

Clinical studies. These should examine whether (i) EAT is a biomarker of CAD, peripheral arterial disease, or cerebrovascular disease, and (ii) whether EAT offers incremental value over traditional CVD risk factors as predictors of cardiovascular outcomes. Because pioglitazone suppresses SCAT macrophage number,[95] a study comparing the effect of a thiozolidenedione on adipokine expression and macrophage content in EAT in patients with DM at CABG would be useful. Biopsies of EAT obtained during CABG should be compared with EAT biopsies from weight-matched controls without

CAD. Lastly, the effect of caloric restriction, weight loss, or pharmacological agents on EAT could be determined by radiological methods such as MDCT.

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Hypertension Intervention Nurse Telemedicine Study (HINTS): Testing a multifactorial tailored behavioral/educational and a medication management intervention for blood pressure control

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Background Only 31% of Americans with hypertension have their blood pressure (BP) under effective control. We describe a study that tests 3 different interventions in a randomized controlled trial using home BP telemedicine monitoring.

Methods A sample of hypertensive patients with poor BP control at baseline (N = 600) are randomized to 1 of 4 arms: (1) control group—a group of hypertensive patients who receive usual care; (2) nurse-administered tailored behavioral intervention; (3) nurse-administered medication management according to a hypertension decision support system; (4) combination of the 2 interventions. The interventions are triggered based on home BP values transmitted via telemonitoring devices over standard telephone lines. The tailored behavioral intervention involves promoting adherence with medication and health behaviors. Patients randomized to the medication management or the combined arm have their hypertension regimen changed by the study team using a validated hypertension decision support system based on evidence-based hypertension treatment guidelines and individualized to patients' comorbid illnesses. The primary outcome is BP control: ≤140/90 mm Hg (nondiabetic) and ≤130/80 mm Hg (diabetics) measured at 6-month intervals over 18 months (4 total measurements).

Conclusions Given the increasing prevalence of hypertension and our inability to achieve adequate BP control using traditional models of care, testing novel interventions in patients' homes may improve access, quality, and outcomes. (Am Heart J 2007;153:918-24.)

Despite the increased incidence of multiple hypertension-related diseases, the availability of respected evidence-based guidelines, only a third of all US hypertensive patients have their blood pressure (BP) under adequate control.[1] Given our inability to achieve adequate BP control using traditional clinic-based physician visits and the potential barriers patients face in obtaining healthcare, interventions that use home BP telemonitoring have the potential to enhance access and improve outcomes for adults with hypertension. We discuss a clinical trial that uses home BP telemedicine monitoring to identify patients with inadequate BP control and then use those values to trigger the intervention.

Most primary care providers know the importance of hypertension; however, there is strong evidence that physicians' threshold for initiating medication changes or increasing dosage is approximately 5 to 10 mm Hg above currently accepted guidelines.[1,2] This tendency of higher threshold has been termed 'clinical inertia.'[3] Patient treatment nonadherence is another major barrier to hypertension management.[4,5] Barriers to adherence such as adverse effects, health literacy, and regimen complexity often are not addressed.[6,7] Strategies designed to overcome clinical inertia and improve patients' treatment nonadherence may improve rates of BP control.

This randomized clinical trial will determine which of 3 nurse-administered interventions, all triggered by

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Table I. Overview of the proposed study design

Intervention arm (sample size)	Usual care (n = 150)	Tailored behavioral intervention (n = 150)	Medication management (n = 150)	Combined intervention (n = 150)
Intervention components	a. Provider-driven care, based in clinic, no special hypertension programs	a. Home BP monitoring evaluated by nurse	a. Home BP monitoring evaluated by nurse	a. Home BP monitoring evaluated by nurse
		b. 11 tailored behavioral modules	b. Medication management intervention	b. 11 tailored behavioral modules c. Medication management intervention

home BP values and delivered in the patients' home, is most effective in improving BP control. To our knowledge, this is one of the largest studies examining the use of home BP monitors in a telemedicine format and using the information obtained from home monitoring to guide clinical decisions.

Design, setting, and recruitment

The Hypertension Intervention Nurse Telemedicine Study trial is testing 3 nurse-administered interventions in a 4-group design: (1) usual care, (2) tailored behavioral intervention, (3) medication management intervention using a validated decision support system (DSS), and (4) combined behavioral and medication management intervention (Table I). Potentially eligible individuals are selected from patients who are enrolled in primary care in 1 of the 3 Durham VA general internal medicine clinics; who have a diagnosis of hypertension based on *International Classification of Diseases, Ninth Revision*, codes; and who are using a BP-lowering medication. An additional inclusion criterion is that patients are required to have inadequate BP control based upon the average of the prior 12-months of clinic BP recordings obtained from electronic medical records. Patients are excluded if they are receiving dialysis; received an organ transplant; hospitalized for stroke, myocardial infarction, coronary artery revascularization, a diagnosis of metastatic cancer, or dementia. Patients are also excluded if they do not have a home telephone or reside in a nursing home, if they receive home health care, or if they have severely impaired hearing or speech. There is 1 laboratory exclusion: serum creatinine >2.5 mg/dL or no creatinine laboratory result in past year. Applying these criteria yields approximately 2700 patients available for enrollment (see Figure 1).

Once patients are identified, their primary care provider sends them a letter describing the study. A research assistant then contacts patients and arranges an in-person meeting at the patients' next primary care provider visit to obtain informed consent and conduct a baseline interview. Consenting patients are then randomized to 1 of the 4 arms using consecutively numbered envelopes; randomization is stratified by diabetic status. Participants are reimbursed $10 each for baseline visit and the 3 subsequent 6-month BP measurements ($40 total). The Durham VAMC Institutional Review Board has approved this study.

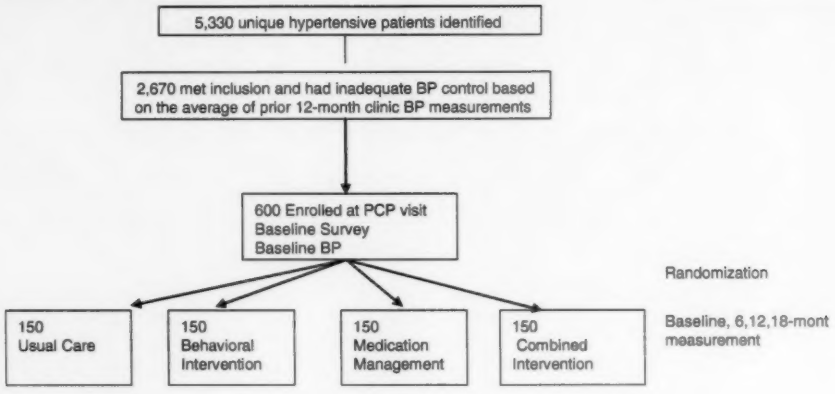
The 3 primary care clinics are staffed by 28 internal medicine faculty physicians and 10 midlevel providers. The Durham VAMC serves a diverse patient population; it is composed of approximately 40% African American patients. We will recruit 600 patients, and all patients will be followed for 18 months.

Telemedicine and home BP monitoring

Encouraging patients to use home BP monitors provides objective information to motivate patients to control their hypertension. Home monitoring also provides documentation of the effects of medications and allows for faster therapy adjustment, which may improve patient adherence to prescribed treatments and subsequent BP control.[8-10] All patients randomized to an intervention arm are provided a wireless home BP monitor (A&D Medical Digital Blood Pressure, Model UA-767PC) and telemedicine device (Carematix Inc, Model #102). The telemedicine device connects to a telephone line like an answering machine. Patient's responses are sent automatically via a toll-free telephone number to a secure server. The nurse can access measurements from the server on a daily basis. By centralizing monitoring and medication management in this way, we believe we may have a greater ability to implement medication recommendations and overcome barriers to care.

Blood pressure measured at home averages 6-8 systolic BP/5-6 DBP mm Hg lower than values obtained during a routine clinic visit.[11] We have chosen to trigger the interventions based on a 2-week average home BP of ≥135/85 for nondiabetics[12] and ≥135/80 for diabetics. Because of the lack of standards for target home BP values for patients with diabetes, the home BP monitoring values used to trigger the intervention for these patients were based upon a panel of hypertension clinicians' recommendations. Deciding not to treat to 5 mm Hg lower values at home was based partially on the concern of treating diastolic BP too low, thereby resulting in symptomatic hypotension.

Figure 1



Study design.

The definition of poor BP control detected by home monitoring is based on an average biweekly BP (minimum of 6 values) that falls above the accepted range. Above average BPs trigger the appropriate intervention depending on group assignment. A safety alert is activated if 2 consecutive home BP measurements are greater than 175/105 mm Hg and separated by a 12-hour period. In this instance, a nurse contacts the patient and initiates the safety protocol.

Tailored behavioral intervention

A multifaceted, comprehensive intervention is being implemented because no single behavioral factor has been shown to consistently improve BP control. The intervention consists of 11 tailored health behavior modules focused on improving hypertension self-management. The use of tailored feedback allows the nurse to address issues that are specifically relevant to a particular patient[13] but in a standardized way.

Hypertension knowledge/risk perception

Patients who do not accurately understand the risks associated with poor BP control receive information from the nurse on the importance of maintaining BP control. Counseling is tailored to individuals who are diabetic,[14] African American,[15,16] recently diagnosed, and/or have hypertensive relatives.[17,18] Risk information is presented using relative risk reduction models, which have been reported to be the most accepted method of presenting risk information for hypertension.[19,20] If identified by the patient as a confidant, a family member/friend may also have the patient's hypertension regimen explained to them.

Memory

Patients identified as having a memory deficit are provided mnemonic strategies to help remind them of the need to take their hypertensive medication consistently and in a timely manner. Memory adherence strategies provided include cueing (eg, pairing taking medication with an established behavior such as brushing teeth) or monitoring (eg, using a calendar to track medication taking). We also provide a weekly pill reminder container.

Social/Medical environment

Individuals who lack adequate social support receive information about potential hospital and community resources, including a toll-free number to assist them in obtaining medications and getting to their doctor appointments.

Patient-provider relationship

For those patients who are classified as having poor patient-provider communication, the nurse explores 4 areas of potential problems: patients feeling rushed, feeling that their provider does not listen to them, not understanding/forgetting information, and feeling that their provider does not involve them in their care. The nurse problem-solves with patients and sets goals of what is reasonable to accomplish at the patient's next provider visit.

Adverse effects of antihypertensive medication

At each phone call in which the patients' BP is out of control, the nurse queries the patient about any hypertension medication adverse effects. If a patient is

experiencing one, the nurse discusses the issue with the patient. The nurse contacts the study physician if a patient reports any potentially life-threatening side effects after instructing the patient to call 911 if the problem represents an emergency.

Health behaviors

Patients are provided the evidence-based recommendations regarding hypertension-related behaviors and are advised on how to reduce behavior risk factors. All patients in our study receive information on caffeine use, salt intake, weight, stress reduction, smoking cessation, and alcohol use. Verbal information is reinforced with mailed handouts.

Diet

The nurse discusses the Dietary Approaches to Stop Hypertension diet, which has been found to lower BP[21] and offers an National Heart, Lung, and Blood Institute-produced handout to reinforce what is discussed.

Exercise

The nurse assesses patients' stage of change for physical activity. Once a patient's stage of change is identified, the nurse can help facilitate the patient's progression and movement through stages.[22] For patients not exercising and not yet ready to change their physical activity level, the nurse explores the reasons for the lack of activity. The nurse provides information about the benefits of increasing physical actively. Among patients who are thinking about changing their activity levels or already changed them, the nurse reinforces these behaviors and problem-solves and addresses any foreseeable barriers that may limit their abilities to start or maintain an exercise regimen.

Smoking

The nurse assesses smokers' stage of change for smoking and tailors patients' progress to cessation. Barriers to initiating and maintaining smoking cessation are explored, and benefits of smoking cessation are emphasized. Local resources including a smoking cessation clinic and medications are provided to patients.

Alcohol

Among those individuals who have one or more drinks a week, the nurse provides information and counseling regarding the relationship between alcohol and hypertension. The nurse also provides local alcohol-related resources.

Stress reduction

This module discusses the relationship between stress and BP and evaluates symptoms related to stress levels. Ways to cope with stress including the benefits of sleep and relaxation/meditation are discussed.

Table II. The Hypertension Intervention Nurse Telemedicine Study behavior module schedule

Encounter 1	Opening, medications, closing
Encounter 2	Medications, side effects, memory
Encounter 3	Medications, side effects, diet
Encounter 4	Medications, side effects, exercise
Encounter 5	Medications, side effects, weight
Encounter 6	Medications, side effects, knowledge
Encounter 7	Medications, side effects, stress, memory
Encounter 8	Medications, side effects, decision making
Encounter 9	Medications, side effects, social support
Encounter 10	Medications, side effects, smoking
Encounter 11	Medications, side effects, alcohol
Encounter 12	Medications, side effects, memory
Encounter 13	Medications, side effects
Encounter 14	Closing

Behavioral intervention schedule. A unique aspect of the tailored behavioral intervention is that the modules are activated only if patients have inadequate home BP control in the prior 2 weeks. If BP control is inadequate, the nurse contacts the patient and discusses material for that particular encounter. The activation frequency of each module varies depending upon how often the patient has poor BP control. Each intervention encounter typically involves 3 to 4 modules (eg, if encounter 2 was activated, the nurse could activate the medication management, side effects, and memory modules, depending on the patients' needs). Each encounter lasts approximately 5 to 10 minutes (see Table II for a schedule of interventions). Once a behavioral encounter occurs, the nurse waits 6 weeks before activating another behavioral intervention. Those patients who maintain adequate BP control will not activate the intervention but will trigger a contact every 6 months to reinforce their positive behavior.

To ensure that the tailored information is standardized, the nurse uses an intervention software application that contains predetermined scripts and patient-specific tailored algorithms. In addition, the intervention application tracks information discussed at each phone call to provide a full understanding of the tailored intervention processes. The duration of each call is recorded for later use in cost-effectiveness analyses. Patients are also able to telephone the nurse with questions related to their hypertension.

Medication management intervention. The medication management intervention is based upon the Assessment and Treatment of Hypertension: Evidence-Based Automation-Hypertension (ATHENA-HTN) program, which was developed to interface with the Veterans Affairs (VA)'s computerized medical record.[23] Unique features of this system include its strong evidence base (protocols are based on a combination of the Joint National Commission 7 and VA guidelines), its ability to tailor recommendations to patients' comorbid illnesses,

and its ability to rapidly summarize hypertension-relevant information for clinicians at the point of care in the VA's Computerized Patient Record System. Many of the clinical rules are based on the following treatment principles: encourage use of thiazide diuretics, which have established effectiveness in reducing long-term morbidity and mortality; select drug partners with favorable interactions; avoid drug partners with potential adverse interactions; avoid drug partners that do not have added efficacy; in patients with additional diseases, select drugs that are appropriate for dual effects; avoid drugs that may aggravate other health problems; and, alert clinicians to potential withdrawal syndromes.

A nurse (supervised by a physician and working within primary care) implements the DSS-generated recommendations based on home BP values. The ATHENA-HTN is a software system that is populated with patients as they are randomized to the medication management arm and combined arm (randomization is rolling). The ATHENA-HTN is connected to the VA's computerized medical record and pulls information on a daily basis (eg, current medications, medical allergies/adverse reactions, laboratory values, diagnostic codes, contraindications to specific therapy, and BP values). If a BP alarm is activated based upon an average of 2-week home BP values, a recommendation is generated immediately. The recommendation is tailored to the patient based upon data from the patients' medical electronic records. Before a change in therapy is made, the nurse examines the patients' medication records to ensure that the patient has been adequately refilling their prescriptions as well as to determine that there are no recent changes in the individuals' hypertension medication. If there is no other explanation for the patients' high BP, the nurse communicates the recommended change to the patient. The study physician generates a note in the patient's medical record and writes an electronic prescription to ensure that the patient has a sufficient quantity of medication or is prescribed any new medication. Once a medication change is completed, the nurse examines VA pharmacy records to verify the patient has received the new medication. The nurse calls the patient 3 weeks after the medication change to assess if there are any adverse effects or patient questions. No additional change in medication will occur for another 6 weeks to allow adequate time for the medication to work unless a BP safety is activated.

Combined (behavioral intervention and medication management). The combined intervention is activated when a patient's BP control is inadequate based upon values obtained from the home BP telemedicine monitor. The nurse initially addresses hypertension medication change based upon the DSS. The behavioral intervention is then activated following the schedule in Table II.

Usual care group. Patients in usual care receive primary care and management of hypertension according to the discretion of their primary care provider. There are no current disease management programs for hypertension, recording and monitoring of home BP, or telephone interventions active in the Durham VA primary care clinics. A Research Assistant blinded to group assignment contacts patients at the 6-month intervals to complete outcome assessment. Usual care patients receive no contact with the intervention nurses.

Study measures

Baseline. Detailed information about the clinical aspects of each patient is obtained using electronic medical records review including patients' most recent body mass index, dates of primary care visits, current medications, and diagnostic codes for visits. An adapted Hypertension Beliefs Questionnaire[24] is used to examine the patient's perceived risk associated with hypertension. Self-reported hypertension adherence is assessed using a 4-item measure.[25] The Rapid Estimate of Adult Literacy in Medicine[26] is used to measure health-related literacy, and memory is assessed as having self-reported challenges remembering to take one's medication. Smoking habits, alcohol use, diet, and the amount of stress and exercise are assessed by patient responses to survey questions. Patients are asked to list adverse effects experienced that are associated with their antihypertensive medication from a standard checklist used in clinical trials. Patients' view of their providers' communication behavior is assessed with a validated measure.[27]

Primary outcome. The primary outcome of the study is BP control measured at baseline, 6, 12, 18, and 24 months using standardized research protocol.[28] At each measurement point, 2 BP measures are obtained using a digital sphygmomanometer[29] after patients have rested for 5 minutes. For each patient's measurement occasion, inadequate BP control is defined as a clinic SBP $\geq$140 mm Hg or a DBP $\geq$90 mm Hg for individuals without diabetes and SBP $\geq$130 mm Hg or a DBP $\geq$80 mm Hg for individuals with diabetes according to the JNC VII/VA guidelines.[1,30] Blood pressure is measured by RAs who are blind to patient group assignment.

Analyses

The primary hypotheses are the following: (1) Patients who receive only the *behavioral* intervention, *medication* intervention, *combined* intervention will show 15%, 15%, and 25% improved rates of BP control, respectively, as compared with the control group over 18 months of follow-up. We plan to use a generalized linear mixed model with a logit link to address the main study hypotheses.[31] Fixed effects in the model will include intervention group, time, and the two-way interaction of group and time; the model will also include patient-level random effects to account for correlation

between patients' repeated measures over time. The proposed analyses focus on an intervention group by time effect in the generalized linear mixed model. In this analysis, we accounted for anticipated improvement in BP control among the usual care group. We will examine the slopes for each intervention group and compare those to usual care. We anticipate that there will be a significantly greater change in slope in the intervention groups relative to the control group (see Figure 2). In addition to our main intervention group hypotheses, we will conduct secondary analyses to adjust for important baseline covariates in our models. Prespecified variables will include sex, age, duration of hypertension, race, and diabetes status. Analyses will be conducted as intent to treat, and sensitivity analyses will examine the implications of the intent to treat assumption.[32]

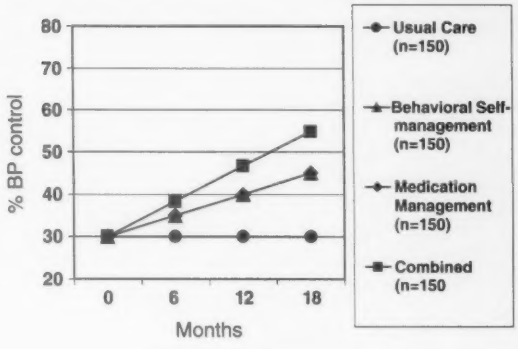
Secondary outcomes

Secondary outcomes of interest in this study include knowledge and perceived risks associated with hypertension. Compared with patients in the usual care and medication management groups, we hypothesize that patients in the tailored behavioral intervention will have greater knowledge and perceived risks associated with hypertension. Knowledge and perceived risks is a continuous measure derived from the modified patient's hypertension beliefs questionnaire.[24] Because the measure is assessed at multiple time points for each patient (baseline, 6 months, 12 months, and 18 months), we plan to use a linear mixed effects model for our analysis.

Medication adherence will be assessed using prescription refill records.[33] Using the method validated by Steiner and Prochazka,[34] we will calculate a Med-Out index that will be equal to (number of days without medication in the observation period) / (total number of observation days). We will calculate the Med-Out for each antihypertensive medication and create an averaged, summary pill refill value. Treatment differences in mean rates of adherence will be examined with a linear regression model.

Sample size and statistical power. An enrollment criterion is that patients must have inadequate BP control based on clinic BP values over the previous year. From our pilot data, however, we estimate that approximately 30% of patients will have their BP in control at the baseline BP assessment by the RA. Based on results from previous studies, we hypothesize that the sample of patients receiving either of the individual interventions will increase BP control by 15% over the 18 months follow-up (see Figure 2). Testing this hypothesis translates into testing a treatment by time interaction in a generalized linear mixed effects model. We estimated the necessary sample size empirically through a simulation study. We expect approximately 15% of the enrolled sample to dropout by the end of the study based on our prior studies. For a type-I error of 0.05 and 80% power, we require a total of 600 patients to be able to detect a 15% increase in probability of BP control.

Figure 2



Expected pattern of results.

Discussion

This study is important for multiple reasons. First, this will be one of the first trials to test a tailored behavioral intervention to improve hypertension adherence head-to-head with a medication management strategy designed to overcome provider inertia. The interventions address both prescribing antihypertensive patterns and changing patients' health behavior and treatment adherence in ways that will enhance generalizability if proven effective. In addition, the trial is also one of the first to use home-based BP measurements to activate an intervention and monitor its effects. Second, patients will be enrolled from primary care clinics where most hypertension treatment decisions are made. Third, the study is one of the largest health behaviors, treatment adherence trials conducted in the United States that will also test long-term effects (18 months). Fourth, we have enrolled over 200 patients thus far, and half are minority patients. Additional strengths of the study include intervention algorithms that can be translated into primary care clinics should they prove to be effective. We are building on previous efforts and testing a novel application of a DSS that has been well developed. We also will assess the costs associated with administering the interventions and examine the policy implications of implementing similar interventions to the large pool of hypertensive patients.

Elevated BP is a major risk factor for cardiovascular disease, and improving BP control levels will decrease morbidity and mortality. Despite the known risk of poor BP control, most adults still do not have their BP under effective control. This study is an important step in testing the effectiveness of 3 interventions to improve

BP control among veterans. If this ongoing intervention is able to achieve levels of BP control similar to those set by national VA goals (or higher), information from this study could directly impact clinical practice.

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Rationale, design, and baseline characteristics of a randomized trial to assess the effect of cholesterol lowering on the progression of aortic stenosis: The Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) trial

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Background Aortic stenosis (AS) is a common health problem in the western world. Recent studies have suggested that cholesterol lowering may have a salutary effect on the progression of AS. The primary objective of the ASTRONOMER study is to determine whether patients with AS randomized to rosuvastatin will experience less progression in AS severity as measured by aortic transvalvular gradients and valve areas. The secondary objectives are to determine the effect of rosuvastatin on the rate of cardiac death and aortic valve replacement and to assess the time to outcome during a follow-up of 3 to 5 years.

Method This is a double-blind placebo-controlled study. Patients with mild to moderate AS are randomized to receive 40 mg/d of rosuvastatin or placebo. Patients with any clinical indication for the use of cholesterol-lowering agents according to the 2000 Canadian guidelines are excluded.

Results Recruitment of 272 patients from 23 Canadian sites was completed in December 2005. Compared with patients with AS in published trials, the patients in the ASTRONOMER study are younger (58.1 ± 13.6 years), have less severe AS (AS jet velocity 3.2 ± 0.4 m/s), and are composed of a great proportion (48.9%) of patients with bicuspid aortic valve.

Conclusions Prevention of the development of severe AS needs to be tested in large randomized studies. Recruitment for the ASTRONOMER trial has been completed and results will be available at the end of 2008. (Am Heart J 2007;153:925-31.)

Aortic stenosis (AS) is a common valvular disease in the western world.[1,2] Its prevalence and often severity increase with age, and AS will be a more important health problem as a result of the increasing life expectancy of the population.[3] Although AS has been traditionally thought to be a passive degenerative process, recent studies suggest that it is the outcome of an active inflammatory process with many similarities to the atherosclerosis process.[4-7] Cholesterol has been implicated in the development of AS in several animal models.[8-10] Cholesterol lowering may have a beneficial effect in patients with AS by preventing or retarding the progression of the disease. Indeed, beneficial effect of cholesterol lowering using a statin has been reported in several retrospective studies.[11-14]

We hypothesize that the progression of AS is a modifiable process and that cholesterol lowering using a statin will retard the progression of AS and delay the need for aortic valve replacement. We have launched a double-blind placebo-controlled study, ASTRONOMER trial, to test this hypothesis. This report presents the trial design and the baseline patient characteristics.

Study design

Objectives

The ASTRONOMER study will examine the impact of cholesterol reduction with rosuvastatin on the progression of AS in patients with mild to moderate AS. Eligible

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Table I. Patient eligibility criteria

Inclusion criteria
- Age between 18 and 82 y.
- Both men and women will be included.
- Mild to moderate AS defined by peak Doppler aortic valve velocity of 2.5-4 m/s.
- Baseline LDL-C value must be within targeted level for all risk categories according to the Canadian Guidelines.[15]
- Baseline triglyceride levels must be within target level for the risk categories.[15]

Exclusion criteria
- Females of child-bearing potential who do not practice adequate contraception (ie, chemical or mechanical methods) and women who are pregnant or breast-feeding.
- Very mild AS defined by peak Doppler AS velocity <2.5m/s or severe AS defined by peak Doppler AS velocity >4m/s.
- Symptomatic AS.
- Greater than moderate aortic regurgitation.
- Significant concomitant mitral valve disease, defined by > moderate mitral regurgitation or mitral valve area <1.5 cm^2.
- A very high risk of coronary artery disease (10-y risk >30%), according to the Canadian Guidelines.[15]
- Patients with diabetes.
- Known coronary artery disease, cerebral vascular disease, or peripheral vascular disease.
- Congestive cardiac failure with New York Heart Association Class III or IV.
- Uncontrolled hypertension defined as either resting diastolic blood pressure >100 mm Hg or resting systolic blood pressure of >200 mm Hg.
- History of homozygous familial hypercholesterolemia or known type III hyperlipoproteinemia (familial dysbetalipoproteinemia).
- Malignancy requiring treatment in the last 2 y, with the exception of squamous or basal cell skin carcinoma.
- Patients who, in the opinion of the investigator, use drugs of abuse or who consume excessive amounts of alcohol.
- Known muscular or neuromuscular disease.
- Serum CK >3 × ULN at visit 2. Subjects with a CK elevation >3 × ULN may have a repeat assay if the elevation can be explained, (ie, recent trauma, intramuscular injections, heavy exercise, or massage).
- Active liver disease or hepatic dysfunction or AST, ALT, or bilirubin >1.5 × ULN at visit 2 (which may be confirmed with one repeat assay).
- Uncontrolled hypothyroidism, defined as TSH >1.5 × ULN at visit 2 or subjects whose thyroid replacement therapy was initiated within the last 3 m.
- Known significant renal impairment, indicated by serum creatinine 200 μmol/L confirmed upon repeat assay.
- History of gastrointestinal disease, eg, Crohn's disease, which may result in impaired absorption of the study drug.
- The use of any prescription medication given to treat dyslipidemia including statins, fibrates, resins, and niacin (>50 mg daily) within 3 m of visit 1 (Table 7).
- On immunosuppressants such as cyclosporin and tacrolimus
- History of hypersensitivity to HMG-CoA reductase inhibitors.
- Treatment with another investigational drug within 30 d of enrolling into this study.
- Any significant disease, which in the opinion of the investigator would render the patient unlikely to complete the follow-up.
- Urine protein/creatinine ratio >56 mg protein per millimole of creatinine or >0.056 g/mmol (SI units) at visit 2.

AST, Aspartate aminotransferase; *ALT*, alanine aminotransferase; *TSH*, thyroid-stimulating hormone; *HMG-CoA*, 3-hydroxy-3-methylglutaryl coenzyme A.

patients will be randomized to receive either a placebo or a fixed dose of the active drug (rosuvastatin, 40 mg daily) for a minimum duration of 3 years. The primary objective is to determine whether patients randomized to rosuvastatin will experience less progression in AS, as measured by a smaller increase in aortic transvalvular gradients and a lesser reduction in the aortic valve area, than patients randomized to placebo. The secondary objectives are to determine the effect of rosuvastatin on the rate of cardiac death or aortic valve replacement during the follow-up period and to assess the time to outcome events between the 2 treatment groups.

A fixed dose of rosuvastatin (40 mg daily) was decided upon instead of a titration protocol to achieve specific targets of total and low-density lipoprotein cholesterol (LDL-C) levels. This simplifies the follow-up visits and better preserves the blinding of treatment assignments. A large enough dose of active agent was chosen to maximize the level of lipid reduction to increase the ability to detect any true difference in the rate of progression. The recruitment phase ranged from 1 to 3 years (average, 2 years) because of the different times taken to activate the individual sites. The treatment duration will be a minimum of 3 years to a maximum of 5 years, with an average follow-up of 4 years. The follow-up will be completed 3 years from the time the last patient was randomized.

Inclusion and exclusion criteria

We included only patients with mild to moderate AS (maximal aortic valve velocity, 2.5-4.0 m/s by continuous wave Doppler). Patients with severe AS (maximal aortic valve velocity, >4.0 m/s) generally have densely calcified valves and a high probability of requiring aortic valve replacement, and also have greater likelihood of adverse events in short-term follow-up. Prevention strategies, such as statin therapy, are therefore unlikely to be efficacious in these patients. Patients with any clinical indication for the use of statin were also excluded (Table I).

Follow-up protocol

After the screening visit, a qualifying echocardiogram was performed at 2 ± 1 weeks and randomization at 3 ± 1 weeks. The patients are followed every 3 months to assess for adverse side effects and to ensure compliance. The fasting lipid profile is measured every 6 months during the first year and then annually for the next 2 to 4 years. The patients' primary physicians and study investigators are blinded to the lipid values during the study, and these physicians have been informed about the study and that their patients' lipid profiles are being monitored in the trial. Creatine kinase (CK) and liver enzymes are measured at the first follow-up visit at 3 months. Patients will be withdrawn from the study but followed for the duration of the trial for clinical events if

Table II. Reasons for withdrawal

Withdrawal of informed consent.
Protocol noncompliance.
Elevation of CK >10 times ULN range and accompanied by muscle pain, tenderness, or weakness.
Persistent elevation of liver enzymes (ALT or AST) >3 times the ULN range.
Deterioration in the patient's condition, which in the opinion of the investigator warrants patient's withdrawal.
LDL-C levels above the upper limits for their risk category, despite taking open-label rosuvastatin 40 mg for an additional 12 wk.
The occurrence of an adverse event, which in the opinion of the investigator warrants patient withdrawal.
Patients who have been unblinded.
Pregnancy.
Newly diagnosed type II diabetes with a fasting blood sugar >7.0 mmol/L.

AST, Aspartate aminotransferase; *ALT*, alanine aminotransferase.

there is a greater than 10-fold increase in CK value or greater than 5-fold increase in liver enzymes compared with the normal values. In patients with a 3- to 10-fold increase in CK or a 3- to 5-fold increase in liver enzymes above normal values, these measurements will be repeated at the next follow-up visit at 6 months. These patients will be allowed to remain in the study.

In addition to the conventional lipid profile, Apo A1, Apo B, and Lp(a) inflammatory markers including high-sensitivity C-reactive protein, interleukin-6, intercellular adhesion molecule-1, and E selectin will also be measured at baseline, 1 year, and the end of follow-up to obtain insights into the mechanisms of progression and responses of the disease to treatment.

Follow-up Doppler echocardiograms are performed annually, and the results will be available to the investigators and the patients' primary physicians. Annual Doppler echocardiograms are obtained to monitor the progression of the disease and for safety reasons. When clinically indicated, additional echocardiograms can be obtained at any time during the study. If symptoms attributable to AS are identified in the follow-up visits, the patient's primary physician will be immediately notified of this development, together with the findings of the latest echocardiogram.

All qualifying and follow-up echocardiograms are locally interpreted, with copies sent to the clinical coordinating center. Randomly selected studies constituting 10% of the total number of studies are reviewed and measurements repeated for the purpose of quality control and determining reproducibility of measurements.

Study organization

The study network consists of 23 Canadian centers. The trial is coordinated by the Chalmers Research Group at the University of Ottawa, Ottawa, ON, Canada. A Steering Committee consisting of the Site Principal Investigators and the Coprincipal Coordinating Investigators is responsible for the overall conduct of the trial. A Safety Monitoring Committee consisting of experienced clinicians and clinical trialists monitors the trial by examining the blinded data on an annual basis. Event Verification Committee helps to define the clinical end points and to verify all outcome events (Appendix A).

Withdrawals and rescue medication

Withdrawals of the patient may occur for valid reasons (Table II), which will be documented. A Doppler echocardiogram will be performed at withdrawal and used as the final measure for the purpose of evaluating the primary outcomes according to the intention-to-treat principle.

In patients whose lipid levels rise above the upper limit of normal (ULN) for their risk category and confirmed by repeat tests 12 weeks later, the study medication will be withdrawn and open-label rosuvastatin 40 mg daily will be initiated. The study blind will not be broken, and the patient will not be withdrawn from the study. If the cholesterol levels continue to be out of range after 12 weeks of open-label therapy, the patient will be withdrawn from the study after completing a study termination visit and will be referred back to the primary care physician to initiate appropriate lipid-lowering therapy.

Unblinding

Unblinding may be done only if clinically necessary to ensure patient safety. All reasons for unblinding must be documented in the patient's chart. Patients can temporarily discontinue study medications (for up to 4 weeks for valid reasons; if longer than 4 weeks is required, this must first be discussed with the coordinating center) without unblinding and restart the study medication as soon as possible. Emergency unblinding envelopes are made available to each center for this purpose.

Ethical considerations

This study addresses the issue of whether progression of AS is preventable by statin therapy. The subjects in this trial will have lipid profiles within the target values according to the Canadian guidelines, which proposed different target lipid values depending on the estimated 10-year risk of developing coronary artery disease using the Framingham data.[15] Patients who have indications for cholesterol-lowering therapy are excluded from the study. Furthermore, if subjects develop conditions that require cholesterol-lowering treatment, they will be withdrawn and treated appropriately by their own physicians. In other words, this study enrolls patients in whom pharmacologic treatment to lower cholesterol levels is not indicated, and thus, it is ethical to randomize them to receive either the active drug or placebo.

Table III. Baseline characteristics of the patients

Characteristics	n = 272
Age (y), mean (SD)	58.1 (13.6)
Male, n (%)	167 (61.4)
Hypertension	75 (27.6)
Current smoker, n (%)	28 (10.3)
Drug history, n (%)	
Aspirin	89 (32.7)
ACE inhibitor	28 (10.3)
β-Blocker	14 (5.1)
Warfarin	0 (0.0)
Height (kg), mean (SD)	81.0 (16.8)
Weight (cm), mean (SD)	169.9 (21.3)
Heart rate (beat/min)	66.6 (9.9)
Sitting systolic BP (mm Hg), mean (SD)	128.7 (15.7)
Sitting diastolic BP (mm Hg), mean (SD)	76.3 (10.5)
Biochemistry	
Total cholesterol (mmol/L), mean (SD)	5.3 (0.9)
LDL-C (mmol/L), mean (SD)	4.3 (10.0)
Cholesterol/HDL ratio, mean (SD)	3.8 (1.1)
Urea (mg/dL), mean (SD)	6.0 (1.8)
Creatinine (mg/dL), mean (SD)	81.0 (16.9)
Fasting blood sugar (mg/dL), mean (SD)	5.3 (0.8)
Rhythm, n (%)	
Sinus	262 (96.3)
Atrial fibrillation/flutter	4 (1.5)
Paced	4 (1.5)
Other	2 (0.7)

ACE, Angiotensin-converting enzyme; *BP*, blood pressure; *HDL*, high-density lipoprotein.

Sample size and data analysis issues

The sample size was calculated based on the following assumptions. Otto et al[16] reported a mean gradient increase of 7 ± 7 mm Hg/y and aortic valve area decrease of 0.12 ± 0.19 cm^2/y. Using these data and assuming linearity, a 4-year follow-up will result in an increase in the mean aortic valve gradient by 28 mm Hg in the control group. With a longer follow-up, the SD of the differences between baseline and final measurements is assumed to be 14 mm Hg. The sample size is calculated to achieve 90% power with 2-tail α of .05 to detect a 7-mm Hg less progression over a period of 4 years. This is a 25% reduction in mean aortic valve gradient in the treatment group (ie, 21 mm Hg progression in the active treatment group after 4 years vs 28 mm Hg progression in the placebo group). Assuming a dropout rate of 20%, a sample size of 264 patients will provide 90% power to detect the difference of 7 mm Hg between the 2 arms. This sample size will also have an acceptable power of about 80% to detect a 33% reduction in the secondary clinical event of cardiac death or aortic valve replacement, assuming an event rate of 38% in the placebo control group during the study period.

Statistical analysis of data will follow the intention-to-treat principle for all main analysis of treatment outcomes. In patients who develop clinical events that lead to withdrawal from the study, the primary echocardiographic outcome measures from the latest annual echocardiogram before the occurrence of events will be used for the main analysis. Analysis by treatment will be carried out in subsidiary analysis for the purpose of obtaining insights into the mechanisms and effects of treatment and for hypothesis-generating purposes. Hemodynamic parameters of AS severity will be compared between treatment groups using *t* test or Wilcoxon rank sum test depending on the parameter distributions. We shall compare the 2 treatments adjusting for baseline covariances using an analysis of variance/covariance for these secondary outcomes if appropriate. Treatment effects across different levels of baseline hemodynamic parameters will be assessed by including the baseline levels in the analysis of variance/covariance models.

Table IV. Baseline echocardiographic and Doppler findings of the patients

Aortic valve morphology, n (%)	
Bicuspid	133 (48.9)
Tricuspid	86 (31.6)
Uncertain	53 (19.5)
Aortic jet velocity (m/s), mean (SD)	3.2 (0.4)
Maximum gradient (mm Hg), mean (SD)	41.0 (11.0)
Mean gradient (mm Hg), mean (SD)	22.7 (7.6)
Aortic valve area (cm^2), mean (SD)	1.2 (0.5)
Aortic regurgitation, n (%)	
Mild	127 (46.7)
Moderate	55 (20.2)
Mitral regurgitation, n (%)	
Mild	121 (44.5)
Moderate	24 (8.8)

Results

Trial progress and baseline characteristics

The trial is registered with Current Controlled Trials Ltd, London, UK (ISRCTN 32424163). Recruitment of 272 patients from 23 Canadian centers started in December 2002 and was completed in December 2005. The baseline characteristics of the patients are shown in Table III. There are no patients with coronary artery disease, cerebral vascular disease, or diabetes because they are excluded from the study. Most of the patients were Caucasian. Asians were initially included, but they were specifically excluded from further enrollment into the study from March 2005 onward because of concern of an increased risk of side effects as a result of higher drug levels when they are exposed to the dose of rosuvastatin used in the trial.[17] Patients of Asian origin enrolled before 2005 are permitted to stay in the study. The echocardiographic findings are shown in Table IV. Aortic valve morphology was determined in 219 patients (80.5%), and bicuspid aortic valve was present in 133 patients (48.9%). The baseline peak and mean AS gradients were 41 ± 11 and 23 ± 8 mm Hg, respectively.

Aortic regurgitation of mild to moderate severity was present in two thirds and mitral regurgitation in over half of the patients.

Discussion

Aortic stenosis is a common valvular disease with insidious progression.[1,16,18,19] When the severity is only mild to moderate, it is well tolerated, but when it progresses to become severe, it confers significant morbidity and mortality.[20,21] Recent studies suggest that AS is an active process that is potentially modifiable.[4-7] Adverse events can be avoided if it is possible to prevent or retard the progression from mild or moderate AS to severe AS. Because lipoproteins are involved in a number of putative pathways in the development of AS, treatment to lower cholesterol represents a reasonable target to reduce AS progression.[22] A number of recent retrospective studies have suggested that statin use was associated with a slower rate of progression of AS.[11-14] A recent open-label prospective study (RAAVE) compared 61 patients with AS started on rosuvastatin (20 mg/d) for elevated LDL-C with 60 patients with AS with normal LDL-C and not receiving statin, showing less AS progression in the patients treated with rosuvastatin.[23] There were differences in baseline characteristics between the 2 groups of patients, and some of these differences might have impacted on the results. Progression of AS was unaffected by intensive lipid lowering using 80 mg of atorvastatin in the Scottish Aortic Stenosis and Lipid Lowering Trial: Impact on Regression (SALTIRE) study, which is the only published randomized study to address this issue.[24]

Several explanations may account for the findings of the SALTIRE study. The sample size was modest (165 patients), and the study included patients with severe AS who are at an advanced stage of the disease and less likely to benefit from lipid-lowering treatment. The median follow-up of 25 months may be too short to detect a difference between the 2 treatment groups because progression of AS is a slow process. Thus, the results of the study cannot be conclusive because of the small sample size and the short follow-up.

Our study has features that are distinctly different from both the RAAVE and the SALTIRE studies. We targeted patients with mild to moderate AS, and our patients appear to have less severe AS (peak gradient, 41 $\pm$ 11 mm Hg) compared with those in RAAVE (54 $\pm$ 19 mm Hg) and SALTIRE (49 $\pm$ 9 mm Hg). Our patients are younger (58 $\pm$ 14 vs 74 $\pm$ 9 years in RAAVE and 68 $\pm$ 11 years in SALTIRE). We have many more patients with underlying bicuspid aortic valve (48.9% vs 0% in RAAVE and 3.2% in SALTIRE). Our patient population may be more representative of patients with AS in the real world, where bicuspid aortic valve is the most common predisposing condition for the development of AS and is present in about half of the patients with AS undergoing valve replacement.[2,25]

In our estimation of sample size, we believe that a difference of 7 mm Hg in progression between the active and placebo groups will be clinically significant. For instance, a patient who has moderate AS with a mean transvalvular aortic gradient of 20 mm Hg and an aortic valve area of 1.50 cm^2 may progress to severe AS with a mean gradient of 48 mm Hg and an aortic valve area of 1.02 cm^2 in about 4 years at the annual rate of progression reported by Otto et al.[16] If our strategy to reduce the progression rate were realized, the mean aortic gradient would be 41 mm Hg with an aortic valve area of 1.14 cm^2 after 4 years. It will be more than 5 years before the onset of severe AS, translating into 1.3 additional years of event-free survival.

In our study, severity of aortic valve calcification is graded by echocardiography and has been reported to predict the rate of AS progression.[26] This approach does not provide a quantitative measure of calcification, which can be better assessed by computed tomography.

The ASTRONOMER study is a randomized clinical trial designed to assess the effect of statin on the progression of AS. Ancillary studies are included to assess the pleiotropic effect of statin beyond cholesterol lowering. We anticipate that this study will not only yield useful data regarding the management of patients with AS but will also give insight into the pathogenesis of AS. Although there are several ongoing studies to assess the effect of cholesterol lowering in AS, we are aware of only one other ongoing randomized trial, the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, which is a multicenter study being conducted in Europe.[27] The primary outcomes are cardiovascular events including myocardial infarction, stroke, and aortic valve replacement. Patient enrollment has been completed, but the findings will not be available until 2008. The findings of the SEAS study are anticipated to compliment that of our study, the results of which will be available at the end of 2008.

Prevention of the development of severe AS is an interesting idea that needs to be properly tested in large randomized studies. Despite the findings of the SALTIRE study, it is premature to reject the lipid hypothesis in AS. Both the ASTRONOMER study and the SEAS study should provide important information on the pathogenesis and management of AS.

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Appendix A

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Rationale, design, and methods for the *Transplant-Eligible MAnagement of Congestive Heart Failure (TMAC) trial: A multicenter clinical outcomes trial using nesiritide for TMAC*

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Background Urgent heart transplant candidates classified as United Network for Organ Sharing status 1B who require continuous infusions of inotropic agents for hemodynamic stability often have hemodynamic, electrical, or multisystem decompensation. This multicenter trial will study both traditional safety and efficacy parameters and the physiologic mechanisms of benefit of the addition to conventional therapy of nesiritide, a recombinant analog of brain-type natriuretic peptide, in this population.

Methods TMAC is a prospective, randomized, parallel, multicenter, double-blind, placebo-controlled study in patients awaiting heart transplantation who meet United Network for Organ Sharing status 1B criteria (N = 120) and receive continuous dobutamine or milrinone through a double-lumen central catheter for at least 3 consecutive days before randomization. Patients will receive standard care and continuous intravenous inotrope therapy plus a 28-day continuous infusion of nesiritide or placebo. There will be up to 6 months of follow-up. Primary efficacy end point will be days alive after treatment without renal, hemodynamic, or electrical worsening at completion. Secondary analyses will evaluate effects on hemodynamics, echocardiographic parameters, endogenous brain-type natriuretic peptide levels, modification of diet in renal disease–calculated glomerular filtration rate, and all-cause and cardiovascular mortality. Two mechanistic substudies will evaluate the effect on iohexol-determined glomerular filtration rate and assess changes in lung mechanics.

Conclusion This investigation will provide key data for clinical profiles of heart transplant candidates bound to inotropic support. It will investigate the efficacy and safety (especially renal) of nesiritide and provide mechanistic insight into benefits of its use for the relief of breathlessness. (Am Heart J 2007;153:932-40.)

Cardiac transplantation remains the definitive treatment for severe end-stage heart failure (HF), but scarcity of donor organs limits cardiac transplantation referrals to only the subset of the most severely ill patients likely to derive benefit.[1-3] Patients classified as United Network for Organ Sharing (UNOS) status 1B (urgent need) require either continuous infusion of an intravenous (IV) inotrope or implantation of a left (LVAD) or right ventricular assist device. Patients with the status IA designation (emergent need) are those who require treatment with multiple or high-dose inotropes or who have a circulatory support device (eg, LVAD) implanted and are in imminent danger of dying. In 2003, 92 patients classified as status 1B died while on the waiting list and in July 2005, and 340 status 1B patients were awaiting a transplant.[4] Furthermore, ventricular assist device use is associated with substantial morbidity and patient loss.[5,6]

Continuous infusion of inotropes is required to maintain hemodynamic stability and preserve extracardiac organ perfusion, but this strategy has challenges. In 2 studies of patients with HF dependent on continuous inotropic support with milrinone and internal cardiac defibrillators (ICDs), 40% to 50% of patients had died

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Table I. TMAC inclusion criteria

Inclusion criteria
• Be ≥18 y of age and meet criteria for UNOS status 1B heart transplant candidate or, if outside the United States, have comparable status (primary transplant, single allograft candidate)
• Receive continuous IV infusion of dobutamine or milrinone through a double-lumen central catheter for at least 3 consecutive days before randomization
• Be willing and able to participate in the study assessments and follow-up procedures
• Agree to use 2 highly effective methods of birth control for the duration of the study if of childbearing potential (both male and female subjects)

Table II. TMAC exclusion criteria

Exclusion criteria
• Have systolic blood pressure <80 mm Hg for the last 3 measurements within 30 d of randomization or clinically significant orthostatic hypotension
• Weigh >130 kg
• Have been treated with commercial nesiritide within 3 d before randomization
• Have a LVAD or be expected to need one during the 28-d study drug treatment period
• Have received placement of a bi-V pacer within 6 wk before randomization
• Have an internal cardiac defibrillator implanted within 72 h before randomization
• Require chronic hemo- or peritoneal dialysis to treat renal failure, or had acute dialysis or ultrafiltration within 7 d before randomization
• Have been diagnosed with an acute myocardial infarction within 30 d before randomization
• Have received antibiotic treatment (not prophylaxis) within 7 d of randomization.
• History of an allergic reaction or sensitivity to commercial nesiritide
• Be pregnant or nursing
• Received therapy with another investigational drug or device within 30 d of randomization
• Have a history of psychiatric disease or drug or alcohol abuse or poor psychosocial support

after hospitalization for HF and ICD discharge by 5 months.[7,8] Hospitalization rates for HF were 62% in the first study[7] and 65% in the second.[8] Tachyarrhythmias, including ventricular tachycardia requiring shock, occurred as high as 13%.[8] Thus, strategies that can provide hemodynamic stability without escalating inotropic therapy would be desirable.

Nesiritide in the management of HF

Human brain-type natriuretic peptide acts on the vasculature, heart, adrenals, and kidneys, serving as a counter to acute cardiovascular stress.[9] Previous human studies have shown that nesiritide produces balanced vasodilatation, coronary vasodilatation in epicardial arteries without coronary steal, decreased myocardial oxygen consumption,[10-13] neurohormonal antagonism, and renal effects.[12,13] Some studies have pointed to beneficial renal effects of nesiritide under controlled clinical conditions, whereas others have not shown this to be the case.[14] In a 6-hour, placebo-controlled comparison study in patients with acutely decompensated HF, nesiritide was associated with significant improvements in the symptoms of dyspnea and fatigue, a decrease in aldosterone, and increase in urine output.[15,16]

In the randomized double-blind VMAC trial, patients treated with nesiritide reported improvement in their dyspnea than patients who received placebo.[17] The FUSION I pilot study pointed to a signal of benefit in high risk patients, a hypothesis under further investigation.[18] Case studies have suggested that nesiritide may improve pulmonary hypertension.[19-23]

Current controversy and need for TMAC

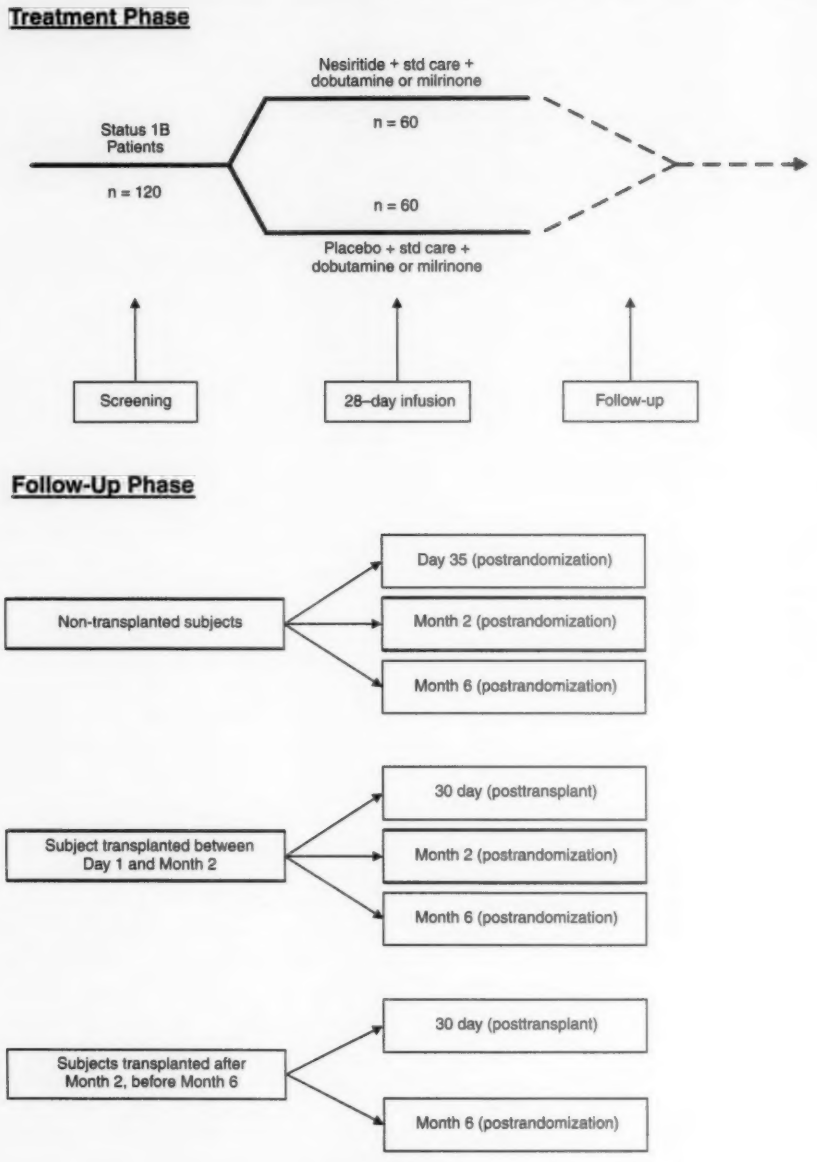
Clinical use of nesiritide has decreased owing to concerns raised by 2 meta-analyses that its use might not favorably affect renal function and mortality. In an opinion article, it was pointed out that previous studies on nesiritide focused on short-term monitoring and did not include adequate clinical follow-up or mortality.[24]

One of the two meta-analyses found an increased risk of worsening renal function with nesiritide, as compared with control groups.[25] The second meta-analysis pointed to increased mortality after pooling 3 randomized, double-blind controlled clinical trials of nesiritide.[26] In contrast, in a pooled analysis of 7 nesiritide clinical trials at 30 days, nesiritide did not significantly increase mortality risk compared to controls.[27] Recently, a panel of cardiologists proposed the following: (1) a large mortality end point trial should be initiated; (2) nesiritide should not be used in intermittent outpatient infusions; and (3) nesiritide should not be used to improve renal function or enhance diuresis.[28]

TMAC design

TMAC is a prospective, randomized, parallel, multicenter, double-blind, placebo-controlled study in patients with status 1B UNOS criteria while awaiting a heart transplant. Patients will be treated with a 28-day continuous infusion of nesiritide or placebo, in conjunction with standard care and continuous IV inotropic therapy. Follow-up is at weekly intervals during the infusion period, 1 week after discontinuation of therapy, and 6 months post randomization. The primary efficacy end point will be days alive without renal, hemodynamic, or electrical worsening. An exploratory end point has been designed to evaluate disease severity using a weighted clinical severity index and scoring system specifically developed for this trial. The study will be

Figure 1



TMAC study design.

conducted at 22 study centers in the United States and Canada and, if necessary, may be expanded to approximately 40 centers. TMAC is registered on ClinicalTrials.gov under #NCT00338455.

Methods

Specific aims

The primary objective of this study in UNOS status 1B cardiac transplant candidates is to assess the safety and efficacy

of nesiritide. The study will evaluate the drug's ability to prevent clinical worsening when administered as a 28-day continuous IV infusion in subjects receiving standard care and continuous IV infusion of dobutamine or milrinone.

Design

Over a 2-year period, 120 subjects will be enrolled. Patients will be de novo cardiac transplant candidates with continuous inotropic support (dobutamine or milrinone) through a double-lumen central catheter for at least 3 consecutive days before randomization. Table I and II list inclusion and exclusion criteria. Figure 1 depicts the trial design. Table III depicts the study schedule and procedures.

Medical management

Patients will be admitted to units equipped for right ventricular catheterization monitoring during screening and randomization, initiation of study drug infusion, and at termination of treatment. Five US centers and all Canadian centers will treat their patients as inpatients. The remainder of US centers will start their patients inpatient but progress to an outpatient basis, unless their status worsens or transplant is performed. If transferred to an outpatient basis, they will by managed by an accredited home infusion and health care service provider to ensure subject safety, provide care standardization, and ensure drug availability. A dedicated project manager will oversee the home services. Home care will be provided by registered nurses who are certified for home infusion of inotropes.

Per protocol patients will have either a double-lumen central catheter or a double-lumen percutaneous central catheter placed for the infusions. Blood draws may be taken from one of the lumens of the double-lumen catheters, or a peripheral site may be used.

TMAC study end points

Safety end points. Safety and tolerability of nesiritide will be assessed descriptively based on adverse events (AEs) and clinical laboratory evaluations. Subjects with AEs or serious adverse events (SAEs) or have significant ongoing laboratory abnormalities at the end of treatment will be followed up until the events resolve or stabilize or until their outcomes are determined. Serious adverse events will be reported and followed up through month 2 post randomization. Hypotension will be included as an AE or SAE assessment and determined to be symptomatic or asymptomatic.

Primary end point. The primary efficacy end point is number of days alive without renal, hemodynamic, or electrical worsening through day 28 (Table V).

Table IV depicts the TMAC Intervention-Based Clinical Severity Index and Scoring System, which provides categories and definitions of worsening. The TMAC Intervention-Based Clinical Severity Index and Scoring System defines severity grades and assigns severity scores to events of clinical worsening. Event severity, from stable to most severe, is graded on a scale of 0 to 6 according to the treatment intervention indicated. This index and a severity score have been applied to each event of clinical worsening (Table V). Only the highest score (reflecting the greatest severity of clinical worsening on that day) will be counted. The sum of the highest daily scores for each subject will be his or her total score at the end of the study and will represent the cumulative clinical severity the subject experiences over the course of the 28-day treatment. This sum will then be divided by the total number of days that the subject receives treatment (an average score). This average score will be calculated for each subject and compared with the average scores for subjects in all treatment groups.

Two additional rules will apply: if a subject discontinues study drug treatment due to clinical worsening, the highest score of 6 will be assigned to the subject on the day of discontinuation and to each day thereafter, through day 28, and if a subject dies during the 28-day treatment period, a score of 6 will be assigned to the subject for the day of death and each day thereafter, through day 28. For subjects who receive a heart transplant during the treatment period, 2 additional rules will apply: subjects with 1B status at the time of transplant will be assigned a score of 0 for all remaining posttransplant days, through day 28, and subjects who change from 1B to 1A status before transplant will be assigned a score of 4 for all remaining posttransplant days through day 28.

Secondary end points. Secondary end points include changes in pulmonary capillary wedge pressure and pulmonary artery pressure (systolic, diastolic, and mean) as measured through day 28. Additional end points to be assessed include domains of the Kansas City Cardiomyopathy Questionnaire and the Short Form 36, the 6-minute walk, cardiovascular death rates, and days in the hospital. Changes in echocardiogram, New York Heart Association classification, vital signs, and right ventricular catheter measurements will also be assessed.

TMAC substudies

Two prospectively defined substudies will be conducted in eligible patients: the Glomerular Filtration Rate (GFR) substudy and the Pulmonary Function Test substudy. The GFR substudy will ascertain whether nesiritide results in an improvement in GFR, as measured by iohexol plasma elimination, when compared to placebo. Changes in iohexol-determined GFR will also be evaluated by fractional excretion of sodium subgroups measured at study baseline. In addition, this substudy will evaluate the accuracy of modification of diet in renal disease (MDRD)–calculated GFRs in these patients.

The objectives of the Pulmonary Function Test substudy are to assess the ability of nesiritide to influence the obstructive component of pulmonary dysfunction, which frequently accompanies severe congestive HF. The rationale for this substudy is to investigate the changes in lung mechanisms into benefits of its use in decreasing breathlessness, by improving pulmonary mechanics.[29]

Data collection and quality assurance

An independent data safety monitoring committee will provide oversight of the study as it relates to the safety of all subjects enrolled. The data safety monitoring com-

Table III. Study procedures and schedule

	Screening (phase 1)	Treatment phase (phase 2)(each day ± 2 d)				
Assessment	**Day 0 (screening)**	**Day 1 (baseline)**	**Day 2**	**Day 3**	**Day 4**	**Day 7**
Hospitalization (for screening randomization, study drug dose initiation, and titration)*	X					
Informed consent and HIPAA authorization	X					
Inclusion and exclusion criteria	X	X				
Demographics	X					
Transplant eligibility (UNOS Status 1B or equivalent)	X	X				X
Serum pregnancy test	X					
Physical examination and cardiac physical assessment	X					
Medical and cardiovascular disease histories	X					
Echocardiogram	X					
6-min walk test	X‡					
NYHA assessment	X					X
ICD interrogation (if appropriate)	X					X
Inotrope administration confirmation	X	X				X
Right ventricular catheterization, hemodynamic measurements		X§				
Vital signs (HR, BP, temperature, and RR)	X	X¶#	X	X	X	X
Body weight and height (height at screening only)	X	X	X	X	X	X
Hydration: cardiac and respiratory status, symptoms of HF	X	X	X	X	X	X
Complications from IV access (inspect and evaluate IV line and IV insertion site)	X	X	X	X	X	X
Concomitant medications, including diuretics, vasodilators, antiarrhythmic medications	X	X	X	X	X	X
Clinical worsening assessment		X			X	X
Laboratory evaluations						
Abbreviated laboratory profile	X					
Hematology, electrolytes, and serum chemistries**		X**				X**
Urinalysis, routine		X				X††
Spot urine tests for urine sodium, urine creatinine, and urine protein concentrations		X				X
Blood collection for serum creatinine, use for MDRD GFR calculation	X	X	X	X	X	X
Blood collection and plasma test for concentrations of BNP and cGMP and serum test for concentrations of N-terminal pro-BNP		X			X	X
Blood collection and test for anti-BNP–specific antibodies‡‡		X				
Investigator's global assessment form		X				X
Subject's global assessment form		X				X
KCCQ		X§§				
Short Form 36		X|||			
Study drug (nesiritide or placebo) infusion initiation and dose escalation and record vital signs		X				

BNP, Brain-type natriuretic peptide; *BP*, blood pressure; *cGMP*, cyclic guanosine monophosphate; *HIPAA*, Health Insurance Portability and Accountability Act; *HR*, heart rate; *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *NYHA*, New York Heart Association; *RR*, beat to beat heart rate interval.

(**Serious adverse event information and mortality assessment, months 2 and 6, by chart review and/or phone contact to obtain information from the subject, responsible relative, clinic or hospital chart, health care personnel, or another individual familiar with the subject).

*A window of up to 7 days is permitted between day 0 (screening, randomization, study drug dose, and titration).

†Nontransplanted subjects only.

‡The 6-minute walk test can be done within 7 days before randomization.

§With proper documentation of results, study centers can use right ventricular catheterization performed within 7 days before randomization without any medication changes.

||With proper documentation of results, study centers can use right ventricular catheterization performed up to 7 days before scheduled test.

¶Take first day 1 vital sign assessment *after* infusion starts.

#Take subsequent day 1 vital sign assessments *after* infusion starts.

**Additional serum analyses for magnesium, cystatin C, C-reactive protein, uric acid, and troponin I.

††Routine urinalysis concentrations of sodium, creatinine, and protein on days 7, 14, 21, and 28 will be used to calculate FeNa.

‡‡A blood sample for anti-BNP–specific antibody testing must be collected at least 3 hours after discontinuation of study drug treatment.

§§Administer KCCQ before or within 1 hour after starting study drug infusion (*before* Short Form 36).

||||Administer Short Form 36 before or within 1 hour after starting study drug infusion (*after* KCCQ).

Treatment phase (phase 2)(each day ± 2 d)			Pretreatment follow-up phase (phase 3)(each visit ± 5 d)		
Day 14	**Day 21**	**Day 28 (termination of treatment)**	**Day 35**	**Month 2**	**Month 6**
X	X	X	X	X†	
		X			
		X			
		X			
X		X			
X	X	X	X		
X	X	X			
X	X	X	X		
		X‖			
X	X	X	X		
X	X	X	X		
X	X	X	X		
X	X	X	X		
X	X	X	X	X	
X	X	X	X		
X**	X**	X**	X**		
X††	X††	X††			
X	X	X	X		
X	X	X	X		
X	X	X	X		
		X‡‡	X		
X	X	X			
X	X	X			
X		X			
		X			

Table IV. TMAC Intervention-Based Clinical Severity Index and Scoring System

Score	Event severity definition
0	Stable at home or inhospital (for subjects treated as inpatients)
1	Unscheduled emergency department visit >24 h (actual hours, not date change) or hospital admission
2	Pharmacological treatment of hemodynamic instability (excluding imminent or ongoing cardiopulmonary arrest/code)
3	Any form of continuous or intermittent hemodialysis or ultrafiltration or intraaortic balloon pump placement
4	Prevention of imminent cardiopulmonary arrest
5	Treatment of cardiopulmonary arrest indicated: code call
6	Death

mittee has the right to receive unblinded information to evaluate safety, but the sponsor and the steering committee members will remain blinded. An independent adjudication committee will review all deaths, hospitalizations, and events of clinical worsening. For both clinical worsening and nonclinical worsening admissions, members of the committee will determine whether the precipitating cause of admission was cardiovascular or renal, a combination of both, or some other cause. Deaths will be reviewed to appropriately assign or classify the cause of death.

Statistical considerations

Sample size and power. The sample size determination for this study is based on the total number of patients in the target population and the rate of enrollment. Approximately 120 subjects will be enrolled to obtain a total of 80 evaluable subjects (subjects who have received at least one dose of study drug and who have the baseline visit and at least 1 postbaseline follow-up visit). Although there is no prior study in this patient population to allow an estimate of this study's power, it is assumed that with the effect sizes of 0.2 (small), 0.5 (medium), and 0.8 (large) and a sample size of 40 per arm, the power will be 14%, 59%, and 94%, respectively, using a 2-sided t test at a significance of .05. If the statistical power is low, caution will be used in interpreting test results that are not statistically significant.

Safety end points. All AEs, SAEs, laboratory tests, and abnormalities will be summarized and statistically compared. Mortality rates will be summarized using Kaplan-Meier plots, and a log-rank test will compare the survival functions between treatment groups. For renal safety, the renal worsening elements through day 28 will be summarized and compared between treatment groups. In addition, the serum creatinine concentration change from baseline will be summarized and compared over time with a repeated measurement analysis method. Creatinine concentration change from baseline may also be categorized and analyzed as categorical variables using the Cochran-Mantel-Haenszel (CMH) test or a logistic regression approach, including the risk factors.

Table V. Assignment of severity index score by clinical event

Indicator event definition	Weighted points for event severity*
Renal worsening	
Dialysis initiation	3
Ultrafiltration initiation	3
Hemodynamic worsening	
Dose increase (≥50%) of IV inotrope or absolute dose increase of dobutamine (≥2.5 μg) or milrinone (≥0.18 μg)	2
Change in baseline inotrope: dobutamine to milrinone or milrinone to dobutamine	2
Addition of second inotrope	2
Addition of IV vasodilator	2
Unscheduled right ventricular catheterization for clinical change resulting in a therapeutic change (excludes protocol requirements and any site's standard prescheduled clinical procedures)	2
Implantation of a ventricular assist device	4
Intubation with mechanical ventilation	4
Implantation or use of another mechanical cardiovascular support device, excluding intraaortic balloon pump placement	4
Electrical worsening	
Appropriate ICD or ECD firing	4
After day 1 (baseline), need for placement of an ICD or ECD (for secondary prevention)	4
New-onset atrial arrhythmia requiring pharmacological or device-based therapy	2
After day 1 (baseline), ventricular arrhythmia necessitating a change in antiarrhythmic medication	2
Emergency cardioversion for hemodynamically significant atrial arrhythmia	4
Hospitalizations	
Unscheduled visit to an emergency department of >24 h (actual hours, not date change), or hospital admission (for subjects treated as outpatients)	1
Code call and death	
All-cause death†	6
Resuscitated cardiac arrest (successful emergency code call)	5

ECD, External cardiac defibrillator.
*Points in this column will be assigned to the subject each day, but only the highest score, reflecting the greatest severity of clinical worsening, will be counted for that day.
†The Clinical events Committee will adjudicate clinical worsening, all-cause deaths, and all-cause hospitalizations.

Primary, secondary, and other efficacy end points. Days alive without clinical worsening will be summarized and analyzed as a continuous variable. A 1-way analysis of variance with treatment in the model will be carried out for continuous variables if the assumptions are satisfied. If the treatment groups differ through day 28, secondary analyses will be conducted to explore the effect of risk factors. In addition, multiple regression models will be explored. For categorical variables, the CMH test of "raw mean scores differ" will be used for ordinal response variables, and the CMH test of "general association" will be used for nominal variables. The Fisher exact test will be used for categorical variables if the cell sizes are sparse and the sample sizes are small. For patient-reported outcome data, such as the Kansas City Cardiomyopathy Questionnaire and the Short Form 36, overall scores and scores for the domains will be computed according to the manuals. Kaplan-Meier estimates and plots will be generated for the time-to-event variables, and the log rank test will be carried out to compare the survival functions for the treatment groups. The relationship between the risk factors and other clinical events will be explored using Cox regression models.

Subgroup analysis. Subgroup analysis will be considered for the following: inpatient versus outpatient, geographic region, blood types, etiology of underlying cardiac disease, ejection fraction <25% versus ≥25%, hemodynamic parameters (blood pressure, heart rate, pulmonary capillary wedge pressure, pulmonary artery pressure), low hemoglobin concentration, presence of ICD, history of atrial fibrillation, inotrope administered at study entry, sex, history of ventricular tachycardia, baseline MDRD-calculated GFR, history of diabetes, and subjects receiving transplant post randomization vs not receiving transplant.

Limitations of the study

One limitation of this trial rests in the lack of prior studies systematically evaluating these advanced HF patients who are subject to clinical worsening and decompensation. These factors may affect recruitment of patients into the study and contribute to early withdrawals. This is why we have selected a sample size of 120 patients, assuming that 80 evaluable subjects will be retained. Although we expect a high effect size due to high event rates per day inherent in this population, the number of patients planned could yield a low power if this expectation is not met. Even so, the data will provide insight into the prolonged infusion effects especially safety and renal effects. In addition, patients with refractory end-stage disease may not be able to sustain hemodynamic stability after nesiritide withdrawal and may require continuous nesiritide infusion to maintain hemodynamic and clinical benefit.

Summary

The TMAC trial will provide the first multicenter study data on outcomes in the pretransplant population and provides an opportunity to study regional practice heterogeneity. In addition, TMAC will provide enhanced evaluation of the effects on mortality and related risk factors from the use of nesiritide, with up to 6 months of follow-up. It is anticipated that TMAC will serve to define the impact of nesiritide on renal function as well as its effect on pulmonary dynamics.

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Preventing tomorrow's sudden cardiac death today: Part I: Current data on risk stratification for sudden cardiac death

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Accurate and timely prediction of sudden cardiac death (SCD) is a necessary prerequisite for effective prevention and therapy. Although the largest number of SCD events occurs in patients without overt heart disease, there are currently no tests that are of proven predictive value in this population. Efforts in risk stratification for SCD have focused primarily on predicting SCD in patients with known structural heart disease. Despite the ubiquity of tests that have been purported to predict SCD vulnerability in such patients, there is little consensus on which test, in addition to the left ventricular ejection fraction, should be used to determine which patients will benefit from an implantable cardioverter defibrillator.

On July 20 and 21, 2006, a group of experts representing clinical cardiology, cardiac electrophysiology, biostatistics, economics, and health policy were joined by representatives of the US Food and Drug administration, Centers for Medicare Services, Agency for Health Research and Quality, the Heart Rhythm Society, and the device and pharmaceutical industry for a round table meeting to review current data on strategies of risk stratification for SCD, to explore methods to translate these strategies into practice and policy, and to identify areas that need to be addressed by future research studies. The meeting was organized by the Duke Center for the Prevention of SCD at the Duke Clinical Research Institute and was funded by industry participants. This article summarizes the presentations and discussions that occurred at that meeting. (Am Heart J 2007;153:941-50.)

Although mortality from cardiovascular disease has diminished in recent years, sudden cardiac death (SCD) remains the most common mode of death in the United States, claiming the lives of up to 350000 people per year.[1-4] To reduce the incidence of SCD, accurate and timely prediction of risk is of paramount importance. Most SCD events occur in persons who do not have previous symptoms or signs of cardiac disease and, as such, would not have been considered to be at an increased risk for SCD.[5,6] Unfortunately, today, there are no tests that have been proven to predict SCD accurately in such persons.

Risk stratification for SCD has been studied primarily in patients with a history of an acute myocardial infarction (AMI) and/or congestive heart failure (CHF). Because survivors of AMI and patients with CHF have long been known to be at an increased risk for SCD, randomized clinical trials of implantable cardioverter defibrillator (ICD) therapy have focused on these patients.[3,6-13] Although most of these trials have shown a significant reduction in SCD and all-cause mortality

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with an ICD, most patients enrolled in those trials did not receive therapy (ICD shock or antitachycardia pacing) during study follow-up.[7,9-12] Some have argued that this observation is evidence that, for many patients, the implantation of an ICD was not necessary; however, this argument does not take into account the trials' limited duration of follow-up.[14] Several tests have been claimed to predict SCD risk in survivors of AMI and in patients with CHF; however, there is little agreement on which test, in addition to the left ventricular ejection fraction (LVEF), should be used in clinical decision making.

The Duke Center for the Prevention of SCD within the Duke Clinical Research Institute conducted a "think tank" meeting on July 20 to 21, 2006, in Washington, DC, to review current data on strategies of risk stratification for SCD, to explore methods to translate these strategies into practice and policy, and to identify areas that need to be addressed by future research studies. Discussions included a review of the available data on risk assessment strategies for SCD with a focus on their validity and generalizability, characteristics of an optimal risk assessment strategy, roles of the National ICD registry, modeling and cost-effectiveness in risk assessment of SCD, and priorities for future research. This article summarizes discussions of data on risk assessment strategies for SCD, the role of the National ICD Registry in SCD risk stratification, and areas that were felt by the participants to be promising areas for additional research.

Assessment of SCD risk: general considerations

One important challenge in studying SCD and its prevention lies in the accurate identification of the event. The definitions of SCD that are most commonly used are necessarily operational and take account of the limited and often circumstantial nature of the evidence available for the task. In addition, SCD is not a homogeneous pathophysiologic entity, but it is the final phenotypic manifestation of a number of unrelated disorders. These 2 factors alone introduce significant difficulties into the clinical study of SCD.

The decision to screen a patient for a high risk of an adverse event, such as SCD, is based on the premise that the identification of a high-risk individual will lead to an intervention that will produce measurable improvement in that person's outcome. Thus, the test must be sufficiently accurate to allow efficient application of the available therapies, the therapies must be sufficiently effective to produce a clinically important reduction in mortality, and the clinical practice community must have reached consensus on the connection between screening test results and indicated effective therapies.

The predictive accuracy of a test is determined by its calibration (reliability) and discrimination. Calibration refers to the agreement between what is predicted by the test and what is actually observed. Discrimination refers to the ability of a test to separate patients who have an adverse event from those who do not. Discrimination is usually measured by concordance probability, or c-index. This index reflects the proportion of all patient pairs in which predictions and outcomes are concordant.[15,16]

Both because of imprecision in identification of preventable SCD events and because of difficulties in predicting this risk distinctly from the risk of death in general, factors that are believed to be good at stratifying the risk of SCD are not necessarily the best choice for directing preventative treatments. The relationship between risk and treatment benefit must, therefore, be validated rather than assumed.[17]

Assessment of SCD risk: specific tests and strategies

Several risk assessment strategies for SCD were discussed at the meeting. Data on these strategies are detailed below.

Left ventricular ejection fraction

Risk stratification. The LVEF has been recognized as a predictor of all-cause mortality in patients with coronary artery disease (CAD) for >30 years.[18-20] One early study by the Multicenter Postinfarction Research Group showed in 866 post–myocardial infarction (MI) patients that the strongest predictor of 1-year cardiac mortality was the LVEF.[20] This finding has withstood the test of time. In the VALIANT, a randomized comparison of captopril, valsartan, and their combination in post-MI patients (n = 14609) with left ventricular dysfunction, CHF, or both, LVEF was a strong predictor of SCD or cardiac arrest. The risk of SCD or cardiac arrest increased by 21% for every 5% decrease in LVEF.[21]

Left ventricular ejection fraction is also a strong predictor of all-cause mortality in patients with nonischemic cardiomyopathy. The MACAS was a prospective cohort study of 343 patients with nonischemic cardiomyopathy and an LVEF ≤45% who were followed for a mean of 52 months. Left ventricular ejection fraction was the only significant predictor of major arrhythmic events with a relative risk (RR) of 2.3 per 10% decrease in LVEF (95% CI 1.5-3.3, $P < .0001$) in patients with sinus rhythm and 4.5 per 10% decrease in LVEF (95% CI 1.5-13.2, $P = .0008$) in patients with atrial fibrillation.[22]

Treatment benefit. Thus, LVEF is the most consistent and one of the strongest predictors of all-cause mortality in patients with ischemic and nonischemic heart disease. Accordingly, a low LVEF (≤35% in most trials)

was the main entry criterion in the large randomized clinical trials of primary prevention ICD therapy. By showing significant improvement in survival with an ICD, these trials have validated the hypothesis that a low LVEF identifies patients who are likely to benefit from an ICD.[7,9-12] However, two thirds or more of the patients randomized to ICD therapy in those trials did not use their ICDs during the limited duration (3-5 years) of the trials. This observation, made using ICD log data in MADIT-II and SCD-HeFT ICD patients, has raised the question of whether it is possible to refine selection of primary prevention patients for ICD therapy by further risk-stratifying patients who are currently considered eligible for ICD therapy based on MADIT-II and SCD-HeFT entry criteria.[10,12]

New York Heart Association class

Risk stratification. Heart failure symptoms, as reflected in the New York Heart Association (NYHA) functional class provide a potent risk stratification tool. Despite its obvious subjective and imprecise nature, this simple bedside assessment remains useful even in the current era of sophisticated tests and biomarkers. Patients with NYHA class II and III symptoms are at a higher risk for SCD than death from progressive pump failure. In contrast, patients with NYHA class IV symptoms are less likely to die suddenly and are much more likely to die of pump failure.[23]

Treatment benefit. These observations have been the subject of ongoing debate, especially in light of the results of SCD-HeFT, in which a subgroup analysis showed significant benefit from an ICD in patients with NYHA class II symptoms but not in those with NYHA class III symptoms.[12] Nevertheless, patients with NYHA class III symptoms were well represented in other trials of ICD therapy and appeared to derive benefit from an ICD. Indeed, an analysis that combined data from the MADIT-I and II, MUSTT, SCD-HeFT, DEFINITE, DINA-MIT, and COMPANION trials showed a significant improvement in survival with an ICD in patients with NYHA class III symptoms (HR 0.66, 95% CI 0.46-0.95).[24]

Although no clinical trials have been exclusively done in patients with NYHA class I symptoms, patients with NYHA class I symptoms were well represented in MADIT-I, MADIT-II, and MUSTT (36%, 37%, and 36% respectively), all of which showed a significant improvement in survival with an ICD.[7,9,10]

Nonsustained ventricular tachycardia

Risk stratification. A few studies have suggested an association between post-AMI nonsustained ventricular tachycardia (NSVT) and an increased risk of mortality; however, the value of NSVT in predicting SCD has not been consistently demonstrated.[25,26] In a large study of 2130 post-AMI patients, although the presence of NSVT on 24-hour electrocardiographic (ECG) recordings predicted SCD, it could not discriminate between risk of SCD and risk of non-SCD. In addition, NSVT was not a significant predictor of SCD in patients with an LVEF ≤35% in that study.[27]

The predictive value of NSVT in patients with nonischemic cardiomyopathy is also uncertain. In MACAS, NSVT was not a significant predictor of SCD.[22] However, further analysis of the MACAS database showed that ≥10 beat runs of NSVT were associated with a higher risk of major arrhythmic events than 5 to 9 beat runs of NSVT or no NSVT (10%, 5%, and 2%, respectively, $P < .05$).[28]

Microvolt T-wave alternans

Risk stratification. Microvolt T-wave alternans (MTWA) is defined as a change in T-wave amplitude, width, or shape that occurs in alternate beats and can be detected with careful computerized signal processing techniques. Although the pathophysiology of this phenomenon in humans remains uncertain, it is believed to reflect both temporal and/or spatial heterogeneity of dispersion of repolarization in the ventricles. This dispersion can be associated with reentrant ventricular arrhythmias.[29,30] Digital processing techniques have been developed to allow the detection of T-wave alternans (TWA) at a microvolt level. Microvolt T-wave alternans is a heart rate–dependent measure with maximal predictive accuracy at sustained regular heart rates between 100 and 120 beat/min.[31,32] These rates can be achieved either by exercise or by atrial pacing.

Microvolt T-wave alternans has been found to be a predictor of ventricular tachyarrhythmic events.[33-35] Data from 19 studies were combined in a meta-analysis involving 2608 patients. Exercise-induced MTWA was found to have a negative predictive value (NPV) of 97.2% (95% CI 96.5-97.9), a positive predictive value of 19.3% (95% CI 17.7-21.0), and an RR of 3.8 (95% CI 2.4-5.9) for arrhythmic events. Patients with an indeterminate MTWA test result were excluded from the analysis. The predictive value of MTWA varied significantly, depending on the type of patients being studied. In post-MI patients, the NPV of MTWA was 99.4% compared with 95.2% in patients with CHF due to nonischemic cardiomyopathy and 91.6% in patients with CHF due to ischemic cardiomyopathy.[35]

Since the publication of this meta-analysis, 2 studies have been published. One study explored the predictive value of MTWA in 768 patients with ischemic cardiomyopathy (LVEF ≤35%) and no prior ventricular tachyarrhythmias. An abnormal MTWA test was associated with a significantly higher risk of all-cause mortality but only a trend toward increased risk of arrhythmic mortality.[36] Another study examined the role of MTWA in patients with either ischemic or nonischemic cardiomyopathy (LVEF ≤40%) and no history of ventricular tachyarrhythmias. An abnormal MTWA test was associ-

ated with a significant increase in the incidence of a composite end point of all-cause mortality or nonfatal sustained ventricular tachyarrhythmias.[37]

Treatment benefit. The SCD-HeFT MTWA substudy[r] examined the role of MTWA in risk-stratifying patients with ischemic or nonischemic cardiomyopathy, NYHA class II or III symptoms, and LVEF of ≤35%. Of 2521 patients enrolled in SCD-HeFT, 490 underwent MTWA testing at baseline. Indeterminate MTWA test was observed in 41% of the patients. The incidence of the composite end point of SCD, sustained ventricular tachyarrhythmias, or appropriate ICD discharges was not significantly different between the alternans-positive and alternans-negative patients ($P = .56$).[38]

The ABCD trial, a noninferiority study comparing MTWA with electrophysiology study (EPS), enrolled 566 patients with CAD, ejection fraction <40%, and NSVT. All patients underwent an EPS and MTWA testing and were divided into 6 groups based on the results of these tests (MTWA+ and EPS+; MTWA− and EPS+; MTWA+ and EPS−; MTWA− and EPS−, MTWA indeterminate, EPS+, MTWA indeterminate, and EPS−). Patients with a positive result on either test had to have an ICD implanted. The primary end point of the study was ventricular tachyarrhythmic events, and median follow-up was 1.9 years. The incidence of ventricular arrhythmic events was 12.6% in patients with MTWA+ and EPS+, compared with 5.0% in patients with MTWA+ and EPS− and 2.3% in patients with MTWA− and EPS−.[39]

One limitation of MTWA testing is the high percentage of indeterminate tests (20%-40%), which is usually due to atrial fibrillation, frequent ventricular ectopy, or patients' inability to exercise or to attain the target heart rate. Other limitations include uncertainty regarding the usefulness of MTWA testing in patients with a prolonged QRS width and uncertainty surrounding the effect of medications, such as β-blockers and antiarrhythmic medications, on the predictive value of MTWA. The greatest limitation of MTWA is the absence of prospective, randomized clinical trials of ICD therapy in which randomization was guided by the result of MTWA testing. Although TWA testing is promising, these limitations, along with the discordant findings from studies to date, support the need for additional data before establishing the use of MTWA in clinical decision making.[31]

Measures of cardiac autonomic modulation

Risk stratification. Many measures of cardiac autonomic modulation have been proposed to risk stratify patients for SCD. These include heart rate variability (HRV), baroreflex sensitivity (BRS), heart rate turbulence (HRT), and deceleration capacity of heart rate.

Heart rate variability. HRV can be measured by calculating time domain indices or performing spectral (frequency) analysis of an array of R-R intervals on 0.5 to 5-minute ECG segments or on 24-hour ECG recordings. An example of a time domain index is the SD of beat-to-beat R-R interval differences within the recording period. Spectral analysis measures not only the amount of variability but also the number of heart rate fluctuations per second.[40] Reduced HRV has been associated with an increased risk of mortality among survivors of AMI.[41] Heart rate variability was examined in such patients in the ATRAMI study. This study enrolled 1284 survivors of AMI within 28 days of their infarction. Mean follow-up was 21 months, and the primary study outcome was cardiac mortality. A low HRV significantly predicted a high risk of cardiac mortality independently of LVEF and spontaneous ventricular tachyarrhythmias. Sudden cardiac death was not examined in that study.[42]

In patients with nonischemic cardiomyopathy, the predictive value of HRV has not been studied adequately. In MACAS, HRV was not a significant predictor of SCD.[22] In a study of 202 patients with severe chronic CHF (median NYHA class 2.3 ± 0.7) and a median LVEF of 24% ± 7%, although a reduced short-term HRV was a powerful independent predictor of SCD and this finding was validated in a sample of 242 similar patients included in the same study, almost half of the patients in the derivation and validation samples had ischemic heart disease.[43]

Baroreflex sensitivity. BRS can be measured by calculating the slope of the relationship between systolic blood pressure and the subsequent R-R interval during a blood pressure rise in response to a bolus injection of phenylephrine.[44] In the ATRAMI study, a low BRS was associated with a significant increase in the risk of cardiac mortality; however, SCD was not examined in that study.[42] The association between BRS and SCD was examined in another study that enrolled 700 survivors of AMI. Baroreflex sensitivity was shown not to predict SCD after a mean follow-up of 43 months.[45] In MACAS, a low BRS was not a strong predictor of SCD.[22]

Heart rate turbulence. Another less studied measure of cardiac autonomic modulation is HRT. Heart rate turbulence measures fluctuations in sinus rhythm cycle length after single premature ventricular depolarization complexes in a 24-hour ECG recording. Heart rate turbulence was evaluated in 577 survivors of AMI in the Multicenter Postinfarction Program and in 614 post-MI patients randomized to the placebo arm in the EMIAT. The absence of HRT after premature ventricular contractions was a significant predictor of all-cause mortality in both patient samples.[46]

Heart rate turbulence was also examined in 884 patients enrolled in the MADIT-II trial using 10-minute

[r] The results of the SCD-HeFT substudy and ABCD were not presented or discussed at the meeting. They were added to the article after they were presented at the American Heart Association scientific sessions in November 2006).

Holter recordings. The primary substudy outcome was all-cause mortality in patients randomized to medical therapy and appropriate ICD therapy in patients randomized to receive an ICD. Heart rate turbulence was not associated with a significant reduction in the primary end point.[47]

In 242 patients enrolled in MACAS, HRT was not a significant independent predictor of major arrhythmic events.[48]

Deceleration capacity of heart rate. Deceleration capacity of heart rate is another measure of cardiac autonomic modulation that quantifies deceleration-related HRV. Deceleration capacity of heart rate was recently evaluated as a predictor of all-cause mortality in survivors of AMI. It was tested in 1455 patients from Munich and was validated in 656 patients from London and in 600 patients in Oulu. During a median follow-up of 24 months, impaired deceleration capacity of heart rate on a Holter monitor was a strong predictor of all-cause mortality that outperformed LVEF and conventional measures of HRV.[49] The association of deceleration capacity of heart rate with SCD was not examined.

Deceleration capacity has not been examined in patients with nonischemic cardiomyopathy.

In summary, some measures of cardiac autonomic modulation are predictive of all-cause or cardiac mortality; however, these measures do not appear to be significant predictors of SCD.

QT interval, QT dispersion, and QT variability

Risk stratification. Although a prolonged QT interval has been linked to an increased risk of SCD, this link seems to be strongest in patients with the long QT syndrome (LQTS).[50-52] Studies in patients with impaired left ventricular function have yielded conflicting results regarding the prognostic value of the QT interval.[53-55]

The prognostic value of QT dispersion and QT variability is likewise unclear. QT variability can be determined by measuring beat-to-beat QT duration using a semiautomated algorithm and adjusting the measurement for heart rate variance. Although a few studies reported no relationship between QT dispersion or QT variability and patient outcomes, data from the MADIT-II trial showed that increased QT variability was associated with an increased risk of ventricular fibrillation (VF) and ventricular tachycardia (VT).[22,56,57] Although a long QT interval, QT dispersion, and QT variability have been shown in a few epidemiological studies to be associated with an increased risk of SCD, they, like other risk stratification tests, have not been proven to be clinically useful.

Signal-averaged ECG

Risk stratification. The signal-averaged ECG (SAECG) is used to detect low amplitude, high-frequency electrical signals at the end of the QRS complex, known as late potentials. Late potentials correlate with local areas of delayed activation in working ventricular myocardium. Because such local areas may constitute part of the substrate (slow conduction) required to initiate and sustain reentry, many investigators have postulated that an abnormal SAECG may be a strong predictor of SCD in survivors of AMI. Although many studies have proven the prognostic value of SAECG in post-MI patients, the positive predictive value of SAECG in all of these studies was <30%.[58-63]

The prognostic value of SAECG was examined in the MUSTT that enrolled patients with a history of CAD, an LVEF ≤40%, and nonsustained asymptomatic VT. In MUSTT, patients with an abnormal SAECG had a significantly higher 5-year rate of arrhythmic death (28% vs 17%, $P < .01$) and all-cause mortality (43% vs 35%, $P < .01$) than did patients with a normal SAECG.[64] SAECG seems to be a relatively specific predictor of arrhythmic events; however, as with other risk stratifying tests, the performance of SAECG alone is suboptimal.The prognostic value of SAECG in patients with nonischemic cardiomyopathy is uncertain. In MACAS, an abnormal SAECG was not a significant predictor of major arrhythmic events.[22]

Electrophysiology study

Risk stratification. The EPS was, for approximately 2 decades, "the gold standard" method for SCD risk stratification in patients with ischemic heart disease. Several studies have shown that post-MI patients with inducible sustained ventricular tachyarrhythmias during EPS had a significantly higher risk of SCD during follow-up.[65-67] Notwithstanding these findings, the 2-year NPV of EPS was only 88% in MUSTT.[9,68] This observation, along with the results of the MADIT-II EPS substudy, have raised doubts regarding the prognostic value of an EPS in patients with ischemic heart disease. MADIT-II enrolled patients who were at least 1 month post AMI and who had an LVEF ≤30%. During a mean follow-up of 20 months, the ICD resulted in a 31% RR reduction in all-cause mortality. In MADIT-II, 593 of 720 patients who received an ICD underwent electrophysiologic testing at baseline. During a 2-year follow-up period, the incidence of at least 1 therapy for either VT or VF was not significantly different between inducible and noninducible patients ($P = 0.4$). The noninducible patients were significantly more likely to receive ICD therapy for VF ($P = .02$), confirming that an EPS is not predictive of SCD.[69]

In patients with nonischemic cardiomyopathy, the EPS does not appear to have any clinical use.[70-73]

Imaging studies

Risk stratification. Data from some investigations suggest that imaging studies are likely to play an important role in SCD risk stratification not only by measuring the LVEF but also by detecting scar. In that

regard, magnetic resonance imaging (MRI) may have the highest clinical use. Improving the accuracy of LVEF assessment with MRI may enhance the role of the LVEF in SCD risk stratification.[74-76] Furthermore, contrast-enhanced cardiac MRI can detect myocardial scars with high precision.[77-80] Because myocardial scar is an important part of the anatomical substrate for malignant reentrant ventricular tachyarrhythmias, the correlation between the presence of myocardial scar and the risk of SCD has been the focus of some investigations. A couple of these investigations have suggested an association between scar surface area or mass as detected by MRI and inducibility of VT on EPS.[79,81] However, the significance of these findings is uncertain especially in light of these studies' small sample size and the EPS's inability to predict SCD.

Correlating MRI findings with spontaneous ventricular arrhythmic events is clinically more useful; however, data on this topic are scant. Although late enhancement detected by MRI was associated with a significant increase in the risk of major adverse cardiac events in 195 patients without prior AMI, ventricular arrhythmias requiring ICD therapy occurred only in 3 patients.[82] Studies linking scar characteristics with risk of SCD are needed.

Genetic testing

Risk stratification. Genetic testing has the potential to aid with SCD risk stratification. Several genetic markers of SCD have been identified in LQTS, Brugada syndrome, arrhythmogenic right ventricular dysplasia, catecholaminergic polymorphic VT, and hypertrophic cardiomyopathy.[83-86] Mutations in cytoskeletal proteins such as dystrophin and desmin have been associated with an increased risk for SCD in inherited dilated cardiomyopathy.[84] No genetic markers of SCD have been identified in patients with CAD, CHF, or ischemic cardiomyopathy. The slow progress in identifying genetic markers of SCD in such conditions may be due to the observation that many genetic changes can result in the same phenotype. To identify genetic variations that are important contributors to SCD risk, large prospective community-based case-control studies are needed. Designing and conducting these studies is fraught with challenges. Not only is a careful prospective determination of the SCD phenotype required, but because SCD is a complex disease phenotype, any search for common genetic markers for SCD will require detailed clinical, mechanistic, ECG, and pathophysiologic characteristics.[83]

It has been suggested that ion channel sequence variations that are the basis for rare inherited syndromes, such as LQTS or Brugada syndrome, contribute to the increased risk of SCD in more common cardiac diseases. In one study, a single mutation in the *SCN5A* gene found in African Americans was associated with a slight increase in the risk of SCD.[85] Future studies are needed to investigate the value of different ion channel sequence variations in predicting SCD in patients with ischemic and nonischemic heart disease.

SCD genomics was the focus of an expert workshop that was convened by the National Heart, Lung and Blood Institute in 2000. The workshop's main objectives were to review data on familial SCD risk, to explore factors that contribute to arrhythmia susceptibility in common cardiac conditions, and to determine how future genetic and population investigations can help advance this science.[84] Many strategies for data generation were proposed, including analyzing existing epidemiological studies such as the Paris Prospective Study and the Seattle Familial Heart study, designing new basic, clinical, and genetic-epidemiological studies, and characterizing clinical SCD phenotypes within "normal" and high-risk populations.[87]

Serum markers

Risk Stratification. A few serum markers of SCD risk have been proposed. One such marker is brain natriuretic peptide. In one study of 521 survivors of AMI, an elevated brain natriuretic peptide level was associated with a 3.9-fold increase in the risk of SCD.[88] This finding needs to be validated by other studies. Another serum marker proposed to have value in the prediction of SCD is C-reactive protein (CRP). In a study of 3435 white men from Germany, although an elevated CRP level was associated with a significant increase in the risk of coronary events, separate data on the risk of SCD were not provided. The relationship between CRP and risk of SCD deserves further study.[89]

Role of the National ICD Registry

When the Centers for Medicare Services (CMS) officials issued the National Coverage Determination on January 27, 2005, to expand coverage for ICD implantation for the primary prevention of SCD, they mandated that data on all such implants in Medicare beneficiaries be entered in a National ICD Registry. The main goal of CMS for the Registry was to determine whether Medicare beneficiaries who meet the clinical criteria identified in the agency's National Coverage Determination derive benefit from primary prevention ICDs. Through a partnership between the Heart Rhythm Society and the American College of Cardiology, the ICD Registry is now part of the American College of Cardiology–National Cardiovascular Data Registry initiative.

Although CMS officials have mandated submission of data only for primary prevention ICDs in Medicare beneficiaries, >80% of the 1200 participating hospitals are submitting data on all ICD implants, including those received for secondary prevention of SCD and those

received by non-Medicare patients. This Registry may offer opportunities to address questions related to SCD risk stratification in different patient populations. Of the data fields captured by the ICD Registry, the following could inform SCD risk stratification: demographics, medical history, risk factors for CAD, QRS duration, LVEF, and EPS. Planning is underway to capture follow-up data, including device firing, on a subset of patients entered into the ICD Registry. In addition, the ICD Registry will be merged with the Medicare Database to get outcomes data on Medicare patients enrolled in the Registry.[90]

Future studies

Future efforts should focus on examining existing and novel markers in patients with ischemic and nonischemic heart disease to identify those who are more likely to benefit from an ICD. Markers that deserve attention include TWA, measures of cardiac autonomic modulation, QT variability, scar characteristics via MRI, and genetic and serum markers. Some of these markers are being examined in the National Institutes of Health–funded MADIT-II risk stratification substudy. This study will enroll 792 MADIT-II–like patients who will be followed up for 2.5 years for the occurrence of appropriate ICD therapy. Future studies of risk markers for SCD will be most valuable if they examine changes in these markers over time.

Because a single test is not likely to have sufficient accuracy, multivariable statistical risk modeling will be needed. After such models are developed, they will require external validation to ensure sufficient reliability and accuracy in the target populations.

Because most SCDs occur in persons who do not have previous symptoms of cardiac disease, it is desirable to develop markers that are useful for SCD risk stratification in the general population. However, even with very accurate tests but a low pretest probability, as occurs in the general population, the false-positive tests will far outnumber the true-positive ones. The risk of such a screening strategy is that subjects who are not actually at increased risk (ie, the false positives) may acquire a new medical label, develop anxiety, and undergo additional testing.

Conclusions

Although many tests of SCD vulnerability have been examined in patients with ischemic heart disease, current data do not support the consistent use of any test, other than the LVEF, to risk-stratify these patients. Efforts should focus on examining existing and novel markers in patients meeting the inclusion criteria of published clinical trials of ICD therapy to identify those who will benefit from an ICD. In that regard, risk modeling will likely be needed. Whether predictors differ significantly between ischemic and nonischemic cardiomyopathy remains unknown. Robust risk stratification strategies are likely once the temporality of risk markers is understood and the most predictive combination of the required techniques is defined. The National ICD Registry could provide some information on SCD risk stratification in different patient populations if long-term follow-up information is linked with the data currently being collected. The identification of asymptomatic subjects in the general population who will experience SCD as their first manifestation of heart disease remains problematic, and no satisfactory solutions have so far been achieved.

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90. www.accncdr.com/WebNCDR/ICD/RESEARCH.ASPX.

Appendix A

Participants in the meeting:

Participants from the Academia: Sana M Al-Khatib, MD, MHS (co-Director), J Thomas Bigger, MD, Alfred Buxton, MD, Robert M Califf, MD, Anne Curtis, MD, Jeptha Curtis, MD, Bernard J. Gersh, MB, ChB, DPhil, Michael R. Gold, MD, PhD, Jeff Goldberger, MD, Stephen C. Hammill, MD, Jeff Healey, MD, MS, Mark Hlatky, MD, Stefan Hohnloser, MD, Raymond J Kim, MD, Kerry Lee, PhD, Daniel Mark, MD, MPH, L. Brent Mitchell, MD, Eric Prystowsky, MD, Gillian Sanders, PhD (co-Director), and Wojciech Zareba, MD, PhD

Participants from the Centers for Medicare and Medicaid Services: Steve Phurrough, MD, MPA

Participants from the US Food and Drug Administration: Norman Stockbridge, MD, PhD, Robert Temple, MD, Bram Zuckerman, MD

Participant from the National Institutes of Health: Robin Boineau, MD, Michael Domanski, MD

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Preventing tomorrow's sudden cardiac death today: Part II: Translating sudden cardiac death risk assessment strategies into practice and policy

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Although current evidence supporting a more precise strategy for identifying patients at highest risk for sudden cardiac death (SCD) is sparse, strategies for translating existing and future evidence into clinical practice and policy are needed today. A great many unanswered questions exist. Examples include the following: At what level of risk for SCD should we pursue further testing or therapy? How should clinical strategies ethically and economically balance alternative outcomes? How can we best translate optimal strategies into clinical practice so as to prevent tomorrow's SCDs? On July 20 and 21, 2006, a group of individuals with expertise in clinical cardiovascular medicine, biostatistics, economics, and health policy was joined by government (Food and Drug Administration; Centers for Medicare and Medicaid Services; National Heart, Lung, and Blood Institute; Agency for Healthcare Research and Quality), professional societies (Heart Rhythm Society), and industry to discuss strategies for risk assessment and prevention of SCD. The meeting was organized by the Duke Center for the Prevention of Sudden Cardiac Death and the Duke Clinical Research Institute. This article, the second of 2 documents, summarizes the policy discussions of that meeting, discusses an analytic framework for evaluating the risks and benefits associated with SCD prevention and risk stratification, and addresses the translation of SCD risk assessment strategies into practice and policy. (Am Heart J 2007;153:951-9.)

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Risk assessment to prevent sudden cardiac death (SCD) and development of evidence-based clinical practice and policy are complex, multidisciplinary tasks. To bring together diverse stakeholders to discuss these important issues, the Duke Center for the Prevention of Sudden Cardiac Death and the Duke Clinical Research Institute conducted a meeting in Washington, DC, on July 20 and 21, 2006. The meeting brought together individuals with an array of expertise in cardiology, biostatistics, economics, and health policy and included representatives from government (Centers for Medicare and Medicaid Services [CMS], National Institutes of Health, Agency for Healthcare Research and Quality, Food and Drug Administration), professional societies (Heart Rhythm Society), and the device and pharmaceutical industries. In part I of this series, we discussed the evidence supporting existing risk assessment strategies. In this article, we summarize the discussions about the translation of risk assessment strategies into practice and policy and priorities for future research.

The need for SCD risk assessment strategies

A major premise of the meeting was that risk assessment strategies need to be reevaluated in light of new evidence about the effectiveness of preventive therapies. Although pharmacological therapy for SCD has failed to demonstrate survival enhancement, several recent randomized clinical trials in primary SCD prevention populations have demonstrated a reduction in total mortality with use of an implantable cardioverter defibrillator (ICD).[1-6] When applied in populations with proven benefit, ICD therapy seems to represent good value for money using conventional benchmarks, despite the high up-front expense of the ICD.[7-9]

Nevertheless, many involved in the care of high-risk patients have expressed concern that the number needed to treat with a primary prevention ICD is too high and that further risk stratification, beyond that used in the trials, must be devised. The basis for these concerns is contained in several observations.

First, although clinical trials demonstrate a mortality benefit at the population level, many of the individual patients in each of the trials did not receive tachycardia therapy from the device during the trial's follow-up period. For instance, in MADIT-II and SCD-HeFT, <40% of patients received an appropriate ICD shock therapy for ventricular arrhythmias during the first 4 years of follow-up.[1,6] In most trials of preventive therapy, the individuals who benefit cannot be identified, even in retrospect; so it is assumed that the benefits of intervention apply equally to all eligible patients. The ICD however is a unique preventive therapy because patients who received no benefit from therapy are identifiable as individuals, namely, those who did not receive appropriate therapy from the device. This clear difference in identifying treatment benefit at the individual level rather than only at the population level provides a unique opportunity for improving patient management through more targeted device implantation. Although the risks associated with ICD implantation and follow-up have been small in the clinical trials, device complications are more common when used in the broad community practice among less selected patients (unpublished data from CMS QNET ICD Registry).[10-12] How to define which patients "need" an ICD is uncertain; and in this paper, we explore a framework for such a definition. We assume that an optimal risk assessment strategy could help optimize patient management and outcomes by better differentiating patients at high or low risk for SCD.

Second, although ICD implantation in specific primary prevention populations may be a cost-effective use of society's resources,[7-9] these analyses assumed all patients in the primary prevention populations had equivalent risk of sudden death and did not evaluate the value of selecting patients most likely to benefit. Furthermore, the patient population potentially eligible for primary prevention is so large that provision of ICD therapy will strain financial resources and the pool of trained personnel. Resource expenditure could be optimized by improved risk assessment.

Finally, although clinical evidence at present supports prophylactic implantation of ICDs in specific primary prevention populations,[1-6] current practice has not followed published recommendations. At present, most patients who might benefit from prophylactic ICD placement do not receive a device. There are several potential reasons for this gap including difficulties identifying patients who would benefit from an ICD, patients with comorbidities that limit potential benefit, the scarcity of qualified providers to implant ICDs and provide follow-up services, the cost of ICD devices, and the skepticism from some providers and patients regarding the value of ICD therapy.[13] Another important potential reason for this gap may be that clinicians and policy makers do not feel that trial evidence can be generalized to real-world ICD use in the community. And finally, the recent release of information on ICD failures may lead patients and providers to be concerned about the reliability of the devices. Evidence-based risk assessment strategies that accurately indicate which patients are at highest and lowest risk for SCD and provide better targeting of populations for primary prevention ICD use might address some of the existing barriers to use of ICDs.

Given the limitations of current stratification strategies for defining patients at risk for SCD, the costs associated with current treatments, our limited health care resources, and the current barriers to widespread implementation of the evidence, development and evaluation of additional risk assessment strategies are needed.

Populations at risk

Risk assessment strategies for the primary prevention of SCD can target 2 distinct patient populations. The first population consists of those patients who are currently perceived as "high risk" and therefore eligible for ICD implantation under current guidelines. In these patients, better risk stratification could in principle enable identification of a subset of these patients perceived to be at high risk in which an ICD is unlikely to be effective. The second population consists of those patients now considered as "low risk" and therefore not currently eligible for treatment. In this population, risk assessment tools could be used to identify a subgroup that would benefit from ICD prophylaxis. The low-risk population includes both the majority of patients and the majority of the annual sudden deaths[14]—yet the incidence of sudden death in this population is the lowest. Because current risk assessment tools[15] have not

yet been demonstrated to have high predictive accuracy, we focused our risk stratification discussion on predicting SCD in high-risk patients with known left ventricular dysfunction.

An "acceptable" risk

The decision to stratify patients by their risk for SCD implies there is a level of risk below which it is acceptable to withhold ICD prophylaxis. During the meeting, we discussed how agreement on an explicit decision threshold of risk is clinically, statistically, and ethically challenging. One critical level is when the risk of SCD over the expected lifetime of the device and the corresponding potential for benefit from the treatment are equal to the risks of ICD therapy.

The ICD-associated risks can be classified into 5 main categories: (1) initial operative mortality and morbidity; (2) system infections and mechanical complications; (3) device malfunctions; (4) impulse generator replacement operative mortality and morbidity; and (5) long-term morbidity and possible mortality associated with pacing or inappropriate shock therapy. These need to be balanced against the benefits of preventing SCD.

The ICD implantation techniques have evolved substantially over the past 2 decades, reducing procedural risk. Recent primary prevention trials showed a very low operative mortality associated with nonthoracotomy ICD implantation (ranging from 0% to 0.5%).[1-6,16,17]

Nevertheless, this low operative mortality may have been influenced by the types of patients, providers, and institutions that participate in clinical trials. The recent release of the initial 18 months of data from the CMS QNET ICD registry indicated that the inhospital mortality of nearly 45000 ICD recipients enrolled in that registry was 0.29% (unpublished data from CMS QNET ICD Registry). It seems reasonable to require that the risk of SCD over the lifetime of the device be greater than this operative mortality for a prophylactic ICD to be recommended.

In addition to operative mortality, there are potential complications associated with the ICD during both the implantation and subsequent follow-up. In the initial data released from the CMS QNET ICD registry, 3.87% of patients experienced a nonfatal ICD complication during the initial implant hospitalization, including pocket hematoma (1.46%), pneumothorax (0.51%), lead dislodgement (1.02%), and cardiac arrest (0.27%) (unpublished data from CMS QNET ICD Registry). Given the nonfatal nature of these complications, it is more difficult to balance the hazard of their occurrence with the risk of SCD.

After the initial hospitalization, ICD devices can malfunction; and replacing the device carries a significant risk of mortality and morbidity. A recent study by Maisel et al assessed ICD generator malfunctions through analysis of Food and Drug Administration annual reports. From 1990 to 2002, 415780 ICDs were implanted in the United States and 8489 ICDs were explanted because of confirmed malfunction. Over the study period, the annual ICD malfunction rate ranged from 7.9 to 38.6 per 1000 implants with a mean of 20.7 per 1000 implants. In addition, ICD malfunction was directly responsible for 31 confirmed deaths during this period.[12] In a recall situation, the risk associated with the existing device needs to be balanced against the risk of ICD impulse generator replacement. The risk of failure of devices under current ICD advisories ranges from 0.009% to 2.6% during variable follow-up periods.[10] The ICD replacement complication rate in this analysis (8.1%) is similar to that observed in large randomized trials (range, 2.5%-15.2%). To offer guidance to providers, the Heart Rhythm Society recently published recommendations concerning device performance policies.[18] Given the life expectancy of primary prevention ICD patients and the longevity of current ICD generators,[19] even without device recalls, many ICD patients will require a generator replacement during their lifetime; and therefore, these risks need to be considered.[11,20]

In addition to careful consideration of the risks associated with ICD prophylaxis, we need to evaluate the benefits of their use. Stratification of patients by their SCD risk does not necessarily correlate exactly with their potential benefit from ICD therapy. Data from ICD logs and other sources, including clinical trial data, demonstrate that ICDs are not 100% effective in preventing SCD.[21] However, for the specific primary prevention populations represented in the positive randomized clinical trials, there is high-quality evidence demonstrating reductions in total mortality ranging from 23% to 55% with an ICD.[1-6] In addition to these mortality benefits, patients may benefit from bradycardia pacing, from the ability to monitor the heart rhythm, or from effects of the ICD on their quality of life. Patients with an ICD may experience improved quality of life because of the reassurance of the probability of rescue or may conversely experience quality of life decrements because of the fear of ICD shocks.[22] In addition, patients who do not have an ICD, despite being candidates, and then survive an arrhythmic event may be left with substantial neurological impairment. The potential effects on a patient's quality of life need to be considered when evaluating the risks and benefits of ICD therapy.

Evaluation of the risks and benefits of prophylactic ICD implantation in a specific population should also consider the risks associated with the risk assessment procedures used to select the treatment patient population. Many of the candidate tools discussed in part I are considered noninvasive. Nevertheless, to be complete, mortality or quality of life effects associated with

patient selection testing need to be included in the risk-benefit analysis.

Decision analytic framework

Given the multiple competing risks and benefits of ICD prophylaxis and of risk assessment testing, we propose a quantitative method to assess and balance the various tradeoffs over the lifetime of the patient. A decision analytic framework can serve this end. Figure 1 shows a schematic representation of a decision analytic framework to determine the role of risk assessment testing in the prevention of SCD and to determine an acceptable risk for SCD within a given population. This framework is generalizable to any risk assessment tool or sequence of tools.

Decision model structure

The initial choice for the decision maker (the patient, health care provider, or policy maker) is to determine whether risk assessment testing should be performed. Patients who do not undergo risk assessment testing have the average risk of SCD for the particular patient population of which they are a member, whereas patients who undergo risk assessment testing will acquire additional information that revises their estimated risk for SCD. The test results could provide information that suggests that the patient has a higher than average risk for SCD. If this increased risk for SCD is sufficient to balance the short-term and long-term risks of implanting an ICD, prophylactic ICD implantation would be recommended. The test results could alternatively provide information that suggests that the patient has a lower than average risk of SCD. If this lower risk for SCD is not sufficient to balance the short-term and long-term risks of implanting an ICD, prophylactic ICD implantation would not be recommended. Such patients would either be treated medically or would be monitored over time for increases in their risk for SCD. The modeling framework also allows determination of the level of SCD risk needed to warrant ICD therapy.

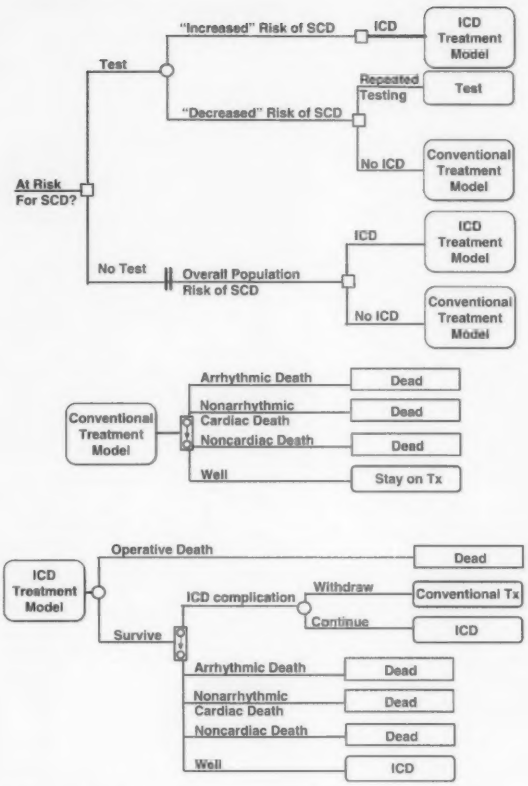
Combination and frequency of risk assessment tests

Although the algorithm presented in Figure 1 considers only the results of a single test, the model can easily be adapted to reflect the results of a panel of tests. The optimal sequence of tests for risk assessment depends on data from existing and future clinical studies.[15]

Sequential testing can be incorporated into the model by updating the patient's pretest probability of SCD after each new test result using Bayesian methods that incorporate prior knowledge about the patient's risk for SCD, the sensitivity and specificity of each test, and the conditional independence of sequential tests.

Of course, decisions to perform a risk assessment test or to treat a specific patient are not necessarily one-time

Figure 1



Schematic of decision analytic framework. The square on the left represents a choice between alternative risk assessment strategies. The decision to test could include an individual risk stratification tool or a sequence of tests. Circles represent chance nodes. Patients who do not undergo risk assessment testing have the population average risk of SCD and would receive ICD therapy according to current recommendations. Those who undergo testing may be identified to be at increased or decreased risk of SCD: Those patients identified at increased risk would undergo ICD prophylaxis and enter the ICD treatment model. Those at decreased risk would be monitored over time according to current recommendations to determine if their risk of SCD has increased to such a level to require ICD therapy. Until such time, these patients are treated according to the conventional treatment model. Patients who receive an ICD are at risk for death from the implantation procedure. Patients who do not die from the procedure and patients assigned to conventional (control) treatment enter the Markov tree (denoted by rectangles containing circles and an arrow). The Markov tree represents the clinical events that can occur during each 1-month period as a patient is followed until death. A patient may die (from arrhythmia, nonarrhythmic cardiac causes, or noncardiac causes). If the patient survives, he or she remains well for the month period. Patients who have an ICD may have a lead infection or failure that may (or may not) cause them to discontinue treatment (and to switch to the control therapy).

decisions. A specific patient's SCD death risk may change over time. Accordingly, the decision analytic framework may also be applied to judge the value of repeated testing in the overall strategy.

Patient preferences

The patient's preferences for different health states should also be included throughout the decision model. These preferences will be determined by information about the health states related to the treatment (eg, quality of life associated with living with an ICD, quality of life associated with having a shock from the ICD), information about the patients' underlying health condition (eg, quality of life associated with the different functional classes), and information about risk assessment testing (eg, quality of life associated with being informed that they are at either high or low risk for SCD). The effects of risk assessment testing itself on quality of life also need to be considered (eg, discomfort or patient inconvenience). Inclusion of patient preferences in the decision analytic framework allows the decision maker to determine not only how the different decisions affect a patient's length of life but also how they affect the quality of this extended life. Such preferences can be included either using community-based average utilities for policy recommendations or individual patient preferences for patient-level decision making.

Time horizon

Although the primary prevention trials have varied in their length of mean follow-up from 16 to 41 months, the risks and benefits associated with ICD implantation do not stop at the end of this trial period. Instead, they continue for the lifetime of the patient. This difference is accentuated by consideration of risk assessment testing especially when no intervention is recommended pending further developments in the patient's natural history. A decision analytic framework, especially one that includes Markov modeling, is able to explore these time-dependent decisions and incorporate changing risks of SCD over time. To evaluate the risks and benefits of different treatment strategies over a patient's lifetime normally requires extrapolation of clinical trial results that often causes concern within the clinical community. However, development of a decision analytic framework allows investigators to explore different assumptions regarding the extrapolation of clinical trial results, to determine whether these assumptions affect treatment recommendations, and to evaluate the advantages of gathering longer-term data.

Sex- and age-specific analyses

Given the composition of existing clinical trial populations, several of the unresolved questions concerning the effectiveness of primary prevention ICD therapy relate to the effects of sex[23] and age on outcome. Are patients above a certain age too old for an ICD? How effective is the ICD in women? As patients age, their mortality due to other causes increases and the relative benefits of the ICD may diminish.[24] Does the competing mortality risk ultimately outweigh the benefits associated with ICD prophylaxis? Such questions can be explored with decision analysis.

Competing mortality risks

Although SCD is a significant mode of death, it is only one of many possible modes of death—and the only one prevented by ICD prophylaxis. The effects of competing risks of mortality need to be considered. Other modes of death can affect the decision analytic framework in several ways. From the outset, patients who are at risk for SCD are also at risk for competing mortality; and although they have an ICD implanted, they can die from other causes. Ideally, patients who are at high risk for SCD but low risk for nonarrhythmic cardiac death and noncardiac death should be selected for ICD prophylaxis.[25] On follow-up, patients who are saved from SCD remain at risk for other causes of death.[17] These competing risks also have implications given a patient's (and his or her family's) preference for the different modes of death. Furthermore, the balance of these different causes of death changes over time as the patient ages. Each of these considerations can be incorporated into a decision analytic framework.

An "acceptable and ethical" risk

Central to the concept of risk stratification of patients at risk of SCD is the expectation that risk assessment strategies will identify some patients as having an SCD death risk that is low enough that an ICD is not recommended. Nevertheless, these patients will not have a zero probability of SCD; and some of these patients will subsequently die suddenly. Although the framework described above attempts to identify an acceptable risk for SCD that would fall below that recommending ICD therapy, it does not determine an *ethical* risk nor does it determine a legal risk for SCD. If risk assessment testing is developed that indicated low risk of SCD, would there be a legal liability if a patient was not given an ICD and then died suddenly?

Conversely, would there be a legal complaint if a low-risk patient had a prophylactic ICD implant that resulted in severe complications? Such ethical and legal issues will need to be discussed before novel risk assessment strategies are widely implemented in the community.

In addition to obtaining informed consent from patients, one step toward resolving these issues would be to involve the various stakeholders (eg, clinical researchers, health care providers, policy makers, payers, and patient representatives) in discussions

regarding the advantages and disadvantages of the risk stratification concept and the corresponding decision analytic framework.

Data needs

Assuming that an acceptable risk of SCD can be determined, high-quality data will be required to apply to the model. Such data will include accurate estimates of the risk of SCD in the population of interest, of the risk of mortality and morbidity associated with ICD implantation in the community, of the benefits of prevention of SCD with an ICD in the community, of the effect of risk assessment and ICD implantation on patient preferences for the various health states, and of the accuracy and reliability of the risk assessment strategies, and consideration of the time-dependent changes in each of these probability estimates in different patient populations.

Although some of the required data have been provided by recent studies including randomized clinical trials, the patients in these trials may not be representative of patients in the community in terms of age, comorbid conditions, or access to follow-up health care.

Similarly, the providers in the trials may not reflect the expertise of those implanting devices in the community. Accordingly, the short- and long-term outcomes of patients receiving an ICD may be different from the populations enrolled in clinical trials. The CMS ICD Registry seeks to address some of these concerns by evaluating risks of ICDs in the community. Although the Registry as it currently exists does not include follow-up data and therefore long-term risks and benefits cannot be evaluated, investigators are actively exploring methods to incorporate into the Registry collection and analysis of such longitudinal data. Such methods range from linking the Registry patient data to national death indices to adjudication of ICD firing data for a subsample of the registry members to determine appropriate shock use and potential benefit of the ICD. The clinical validity of ICD therapy as a surrogate end point for death remains controversial.[26,27]

Data regarding the risk assessment tools themselves will also be required. Data regarding the discrimination capacity (accuracy) and reliability (calibration) of risk stratifying tests are available. These data have been supplemented by observations made with respect to certain risk stratifying tests in the randomized clinical trials, including left ventricular ejection fraction, QRS duration, and functional class. A formal meta-analysis of the 8 primary prevention trials explored the effect of the ICD on total mortality in specific subgroups defined by left ventricular ejection fraction and QRS duration.[28] Additional information concerning the predictive value of clinical characteristics could be obtained through a patient-level analysis of these same primary prevention trials.

Although existing trials may be used to generate hypotheses, further evidence must be gathered through prospective clinical trials. Nevertheless, future trials will be more constrained if the equipoise is lacking to randomize currently eligible patients to no ICD therapy even after a demonstration of low risk for SCD by risk stratification testing.

Some investigators believe that the principal issues related to risk assessment strategies do not require clinical trials but rather can be examined using clinical registries to correlate test results with patient outcomes over time. Although registries are simpler and less expensive than randomized clinical trials, this approach requires identification of large populations in whom risk stratification tools have been applied and in whom clinical outcomes are known.

Statistical modeling could then be used to evaluate the database for a risk stratification test (or combination of tests) that identifies patients whose risk of SCD is so low that they are unlikely to benefit from ICD prophylaxis.

The role of cost-effectiveness in risk stratification

The decision analytic framework discussed above concentrated on the mortality and morbidity risks and benefits associated with ICD implantation and the prevention of SCD without consideration of the cost implications of various strategies. Of course, each of the strategies has associated costs. Although important, determining the costs of a particular strategy is not sufficient, for these costs must be judged in the context of competing needs in the health care system.

Are ICDs cost-effective when used in primary prevention populations? Could risk assessment strategies help us use our limited resources more efficiently? The answer to the first question seems to be "yes" in certain specific patient populations and under certain specific assumptions.[7-9] The answer to the second question is uncertain. It is assumed that the use of noninvasive, low-cost risk assessment strategies will identify patient populations that have increased risk for SCD and for which the cost-effectiveness of ICD treatment is improved. Nevertheless, it is important to remember that a cost-effective intervention does not usually represent cost savings and will require additional resources. If ICDs were implanted only in populations in which existing clinical trials and available data have shown acceptable cost-effectiveness, the additional health care resources required in the United States could be several billion dollars per year.[8] Within currently indicated populations, it may be possible, using risk assessment testing, to identify subgroups that benefit more or less from ICD treatment, thereby improving the cost-effectiveness of ICD implantation in more targeted populations.

The cost-effectiveness of candidate risk assessment strategies to target ICD implantation depends on several factors. First, it depends on the cost-effectiveness of the ICD itself in the targeted population. Previous research has demonstrated that ICD therapy is cost-effective in secondary and primary prevention patient populations provided that the risk of SCD is sufficiently high and provided that the effect of the ICD on total mortality was significant.[7-9,29,30]

Second, the cost-effectiveness of a risk assessment strategy depends on the current penetrance of ICD treatment in the absence of use of the risk assessment strategy. As noted above, only 15% to 20% of those patients eligible for an ICD are currently receiving one. If the patient population receiving an ICD represents those within the larger population at the highest risk of SCD, then a risk assessment strategy that identified these same patients for targeted ICD treatment would merely add costs and morbidity. However, it is likely that the current process of identifying those patients who receive ICD prophylaxis is not optimal and formal risk assessment strategies could be beneficial. Third, the cost-effectiveness of ICD treatment targeting strategies depends on both the cost and morbidity associated with the risk assessment strategy itself. Although the morbidity associated with most risk assessment tests is small, the costs are not. Although these costs are small compared with the estimated $25 000 cost of implanting an ICD, they do need to be considered. Fourth, the cost-effectiveness of a risk assessment strategy obviously depends on the accuracy of the strategy for stratifying a population of interest according to their SCD risk. As indicated in the discussion of decision analytic frameworks and in part I of this series,[15] further research is needed to find an optimal test. Finally, the cost-effectiveness of any risk assessment strategy depends on the overall risk of SCD in the population being tested.

Each of these factors can be included in a decision analytic framework to allow the model to determine not only the most effective strategy but also the most cost-effective strategy. Again, the ethics of using such a model to determine who receives ICD therapy must be considered. It is one thing for a provider to recommend against a treatment or for a payer to deny a treatment to a patient because therapy provides no benefit or because the risks outweigh the benefits; however, it is another matter entirely to deny therapy simply because it costs too much. Cost-effectiveness analysis is predicated on the concept of diminishing returns.[31] With increasing resource use, the clinical benefit eventually becomes too small to justify its costs and health risks. Although the explicit rationing of health care dollars is currently opposed in the United States, most of the obstacles to the wider use of cost-effectiveness analyses in policy formation are not methodological but rather are matters of politics, process, and leadership. The United States is a notable exception to a global movement to use cost-effectiveness analyses to inform health care decisions.[32] A decision analytic framework for considering the costs and benefits of ICD implantation for the prevention of SCD and risk assessment strategies to target therapy use could make the tradeoffs between costs and outcomes explicit and open for an evidence-based discussion.

Future research priorities and conclusions

In addition to research into the accuracy and reliability of risk assessment strategies,[15] there are several other areas of research that will help enable effective translation of risk assessment strategies as they are developed into authoritative clinical practice guideline and policy.

First, a formal decision analytic framework would help the health care community (policy makers, providers, and patients) to evaluate the risks, benefits, and costs associated with risk assessment strategies and ICD implantation. This article provides an overview of such a framework and its different structural and analytical components. Implementation of this framework is needed.

Second, once this framework is developed, necessary data elements will need to be gathered not only from randomized clinical trials but also from registries and databases. A formal meta-analysis of the patient-level data from the existing clinical trials would allow expanded exploration of the risks and benefits of ICD therapy for specific clinical subpopulations. In addition, several clinical trials studying the use of risk assessment strategies in ICD therapy are discussed in part I of this series;[15] their ongoing findings need to be incorporated into the framework. Finally, the development and analysis of the CMS ICD Registry will provide currently missing data on the safety of ICD therapy in the broad community. The proposed linkage of the current Registry to long-term follow-up data will also offer much needed data concerning ICD effectiveness and associated outcomes in patient populations underrepresented in the existing clinical trial literature.

Finally, the development of high-quality recommendations for the prevention of SCD will be of little value unless the recommendations are then implemented into practice and policy. Dissemination barriers may exist at the patient, provider, institutional, and policy levels. Additional research is required to assess such barriers (and potential facilitators) to effective disseminations of developed recommendations. Inclusion of relevant stakeholders in the development and dissemination of risk assessment strategies for ICD therapy will be a necessary component of any implementation effort.

Although ICD therapy has been demonstrated to be effective at preventing SCD in specific populations, risk

assessment strategies have the potential to increase this benefit while lessening its strain on our economic and clinical resources. Optimal evidence-based care requires the development of a framework for establishing what populations and risk level of SCD would benefit from ICD therapy, determining what tests can best accurately identify these populations, and then working to disseminate the needed therapy to all members of this population and their caregivers in an equitable and efficient way.

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Appendix A

Participants in the meeting

Participants from the Academy: Sana M. Al-Khatib MD, MHS (Co-Director); J. Thomas Bigger, MD; Alfred E. Buxton, MD; Robert M. Califf, MD; Mark Carlson, MD; Anne Curtis, MD; Jeptha Curtis, MD; Bernard Gersh, MB, ChB, DPhil; Michael Gold, MD, PhD; Jeffrey Goldberger, MD; Stephen Hammill, MD; Jeff Healey, MD, MSc; Mark Hlatky, MD; Stefan Hohnloser, MD; Raymond Kim, MD; Kerry Lee, PhD; Daniel B. Mark, MD; L. Brent Mitchell, MD; Eric Prystowsky, MD; Gillian D. Sanders, PhD (Co-Director); Wojciech Zareba, MD, PhD.

Participant from the Center for Medicare and Medicaid Services: Steve Phurrough, MD, MPA.

Participants from the National Heart, Lung, and Blood Institute: Robin Boineau, MD; Michael Domanski, MD.

Participant from the Agency for Healthcare Research and Quality: Elise Berliner, PhD.

Participants from the US Food and Drug Administration: Norman Stockbridge, MD, PhD; Robert Temple, MD; Bram Zuckerman, MD.

Participant from the Heart Rhythm Society staff: Joel Harder

Participants from Industry: Dale DeVries; Eric Fain, MD; Ali Haghighi-Mood, PhD; Steve Ketchum, PhD; Philip Sager, MD; Dan Schaber, PharmD; Robert Shalwitz, MD; Joseph Smith, MD, PhD; Michael Stein, MD; David Steinhaus, MD; Steve McQuillan, MS; Marcus Mianulli, PhD.

Coordinating staff: Marelle Molbert and Cass Finley from the Duke Clinical Research Institute.

Interventional Cardiology

Interactions between heparins, glycoprotein IIb/IIIa antagonists, and coronary intervention. The Global Registry of Acute Coronary Events (GRACE)

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Objectives The purpose of this study is to evaluate hospital mortality and major bleeding rates among patients receiving low molecular weight heparin (LMWH), unfractionated heparin (UFH), or both, and to investigate whether concomitant glycoprotein (GP) IIb/IIIa antagonists and coronary intervention affect patterns of use and outcomes with different heparins.

Background With widespread use of glycoprotein (GP) IIb/IIIa inhibitors and invasive treatments, patients with high-risk acute coronary syndrome (ACS) may have a greater bleeding risk and may not gain additional benefit from LMWHs. The purpose of this study is to evaluate hospital mortality and major bleeding rates among patients receiving LMWH, UFH, or both, and to investigate whether concomitant GP IIb/IIIa antagonists and coronary intervention affect patterns of use and outcomes with different heparins.

Methods Data were analyzed from 28 445 patients with ACS; 21 287 had non–ST-segment elevation myocardial infarction or unstable angina and received LMWH or UFH.

Results Fifty-one percent of patients received LMWH, 32% UFH, and 17% both. The lowest inhospital mortality and bleeding rates occurred with LMWH (2.7% and 1.8% vs UFH, 4.1% and 2.7%; all $P < .0001$). After multivariable analysis, LMWH was associated with lower inhospital mortality rates in patients not treated with GP IIb/IIIa antagonists, irrespective of whether they had a percutaneous coronary intervention (PCI) (odds ratio 0.77, 95% confidence interval 0.63-0.94 without PCI vs odds ratio 0.45, 95% confidence interval 0.21-0.98 with PCI). Excess bleeding occurred with PCI in LMWH-treated patients. Patients older than 75 years who received GP IIb/IIIa antagonists and any antithrombotic but not PCI had an increased risk of major bleeding (LMWH 14%, UFH 8.3%).

Conclusions In patients with non–ST-elevation ACS without GP IIb/IIIa antagonists, LMWH was associated with a lower mortality rate and more bleeding episodes in PCI-treated patients than UFH; no differences occurred with GP IIb/IIIa antagonists. Elderly patients managed medically with GP IIb/IIIa antagonists and either heparin had a very high major bleeding risk. (Am Heart J 2007;153:960-9.)

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Treatment with the low molecular weight heparin (LMWH) enoxaparin, or the combination of glycoprotein (GP) IIb/IIIa inhibitors and unfractionated heparin (UFH), along with early intervention strategies, substantially reduce 30-day outcomes in acute coronary syndromes (ACS).[1-3] Low molecular weight heparin is associated with better outcomes than UFH.[1,4] However, in the contemporary era, thought to be characterized by more widespread use of GP IIb/IIIa inhibitors or invasive treatment, patients with high-risk ACS may be at a greater risk of complications and may not obtain any additional benefit from LMWHs.[5,6] The SYNERGY trial[7] showed that the LMWH enoxaparin was noninferior to UFH in the management of aggressively treated patients with high-risk ACS. However, enoxaparin was associated with an increased risk of

bleeding, attributed to crossovers between UFH and LMWH.[7] In the A-to-Z trial, during which background treatment included tirofiban and in which 60% of patients had angiography, LMWH was associated with a nonsignificant reduction in ischemic end points.[8] Bleeding rates, although low, were nonsignificantly greater in patients treated with LMWH.

In this study, we sought to determine whether the findings from the SYNERGY and the A-to-Z trials reflect those observed in the "real world," where physicians can select therapies they determine to be clinically appropriate.

Methods

The GRACE is an observational study designed to reflect an unselected population of patients with ACS.[9,10] A total of 113 hospitals in 14 countries located in North and South America, Europe, Australia, and New Zealand have contributed data to the study.

Adult patients (≥18 years) admitted with a presumptive diagnosis of ACS were potentially eligible for inclusion. Eligibility criteria were clinical history of ACS accompanied by ≥1 of the following: electrocardiographic changes consistent with ACS (ST deviation, or new T-wave inversion >1 mm, Q waves or left bundle-branch block), serial increases in serum biochemical markers of myocardial necrosis, and/or documented coronary artery disease. The qualifying ACS must not have been precipitated by a significant noncardiovascular comorbid condition.

Enrolling sites were encouraged to recruit the first 10 to 20 consecutive eligible patients each month. Demographic characteristics, medical history, presenting symptoms, prehospital delay, biochemical and electrocardiographic findings, treatment practices, and hospital outcome data were collected.[9]

All cases were assigned to one of the following: ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), or unstable angina (visit www.outcomes.org/grace for full definitions). This analysis was restricted to patients with non-ST-elevation ACS (NSTE ACS, including NSTEMI and unstable angina). Patients transferred into a GRACE hospital from a nonparticipating hospital, and individuals who received neither heparin were excluded.

Statistical methods

Comparisons between the respective groups were made using χ^2 tests for categorical variables and Kruskal-Wallis test for continuous variables. Continuous variables are reported as medians (25th, 75th percentiles); categorical variables are reported as percentages. Logistic regression models were constructed to test the associations between LMWH, UFH, both heparins, and hospital death and major bleeding, adjusting for the GRACE risk models for inhospital mortality[11] and bleeding.[12] All tests were double sided and considered significant at $\alpha \leq .05$. The statistical analysis was performed using the SAS software package (version 8.1; SAS Institute, Cary, NC).

Results

A total of 28 445 patients with NSTE ACS were enrolled between April 1999 and March 2005. After exclusions (3123 transfers and 4035 without heparin), the study population comprised 21 287 patients of whom 10 650 were diagnosed with unstable angina and 10 637 with NSTEMI. Patients were divided into groups according to whether they received UFH only (32%), LMWH only (51%), or both (17%). Of the patients who received LMWH only, 89% received enoxaparin (84% of patients who received both UFH and LMWH).

Baseline characteristics and inhospital management by type of heparin received

Of those with NSTEMI, 3235 (30%) received UFH only, 5264 (50%) received LMWH only, and 2138 (20%) received both. The corresponding figures for patients with unstable angina were 3585 (34%), 5575 (52%), and 1490 (14%).

Patients given UFH alone had a higher incidence of clinically important prior and current comorbidities compared with those given either LMWH alone or both heparins (Table I). However, the GRACE risk score for inhospital death[11] was similar for patients receiving UFH and LMWH and was highest for patients given both heparins (Table I).

The use of aspirin was similar irrespective of the type of heparin given. Differences in use of cardiac medications between groups are illustrated in Figure 1. Coronary angiography, revascularization, and GP IIb/IIIa inhibitors were used least frequently in patients receiving LMWH and most frequently in patients receiving both heparins (Figure 1).

Baseline characteristics and inhospital pharmacologic management by treatment received

Neither percutaneous coronary intervention nor GP IIb/IIIa antagonists. Compared with the overall population, patients who did not undergo percutaneous coronary intervention (PCI) or receive GP IIb/IIIa antagonists were less likely to be male, and they had the highest GRACE risk score (127) (Table I). Patients assigned to UFH only had a higher incidence of prior morbidities, reflecting the pattern seen in the overall cohort (Table I). The risk score was higher in patients who received UFH (125) than in those who received LMWH (122) and was highest in patients who received both (127). Patients given LMWH alone were more likely than those given UFH to receive thienopyridines (LMWH alone, 31% vs UFH, 19%) and less likely to receive warfarin (LMWH alone, 5.2% vs UFH, 7.1%) or a fibrinolytic drug (LMWH alone 2.0% vs UFH 4.8%) (all $P < .0001$).

Percutaneous coronary intervention but no GP IIb/IIIa antagonists. Patients who had PCI but received no GP IIb/IIIa antagonists were slightly younger and more likely to be male than the overall population and patients who received neither (Table I). Their risk of inhospital death as determined by the risk score was lower than that for the overall population (117 vs 123).

Table I. Baseline characteristics by management strategy

	LMWH only	UFH only	Both	*P*, LMWH vs UFH	*P* (3-way)
All patients (n)	10839	6820	3628		
Demographics					
Age (y)*	68 (57, 76)	67 (56, 76)	67 (57, 75)	<.001	<.0001
Male (%)	65	64	69	.53	<.0001
Weight (kg)*	76 (66, 86)	78 (68, 90)	77 (68, 87)	<.0001	<.0001
ACS diagnosis					
NSTEMI	49	47	59	.14	<.0001
Unstable angina	51	53	41		<.0001
Medical history (%)					
Angina	65	65	65	0.65	.90
Bleeding	1.0	1.7	1.2	<.0001	<.0001
CHF	10	16	11	<.0001	<.0001
Diabetes	25	30	25	<.0001	<.0001
Hyperlipidemia	51	53	51	<.01	<.01
Hypertension	62	70	63	<.0001	<.0001
MI	35	40	34	<.0001	<.0001
PAD	10	12	12	<.01	<.001
Renal dysfunction†	6.9	10	9.0	<.0001	<.0001
Stroke	7.9	9.8	7.8	<.0001	<.0001
PCI	19	24	20	<.0001	<.0001
CABG	14	19	15	<.0001	<.0001
GRACE risk score*	121 (99, 149)	120 (96, 148)	123 (100, 149)	.01	<.01
No PCI, no GP IIb/IIIa antagonists (n)					
n	7957	4271	1919		
Demographics					
Age (y)*	69 (58, 77)	68 (58, 77)	69 (59, 76)	.14	.31
Male (%)	38	39	35	.13	<.01
Weight (kg)*	69 (58, 77)	68 (58, 77)	69 (59, 76)	<.01	.03
ACS diagnosis (%)					
NSTEMI	46	42	51	<.0001	<.0001
Unstable angina	54	58	49		<.0001
Medical history (%)					
Angina	68	67	69	.25	.21
Bleeding	1.1	2.0	1.4	.0001	<.001
CHF	12	20	15	<.0001	<.0001
Diabetes	26	30	26	<.0001	<.0001
Hyperlipidemia	50	50	50	.88	.99
Hypertension	64	72	67	<.0001	<.0001
MI	37	43	39	<.0001	<.0001
PAD	11	11	13	.17	<.01
Renal dysfunction	7.8	12	9.8	<.0001	<.0001
Stroke	8.7	11	8.5	<.001	<.001
PCI	17	20	16	<.0001	<.0001
CABG	14	19	15	<.0001	<.0001
GRACE risk score*	122 (100, 151)	125 (99, 154)	127 (103, 154)	<.01	<.01
PCI without GP IIb/IIIa antagonists (n)	1468	728	682		
Demographics					
Age (y)*	65 (55, 73)	64 (55, 74)	66 (56, 73)	.61	.59
Male (%)	73	71	73	.22	.44
Weight (kg)*	78 (68, 86)	77 (68, 88)	76 (67, 85)	.34	.27
ACS diagnosis (%)					
NSTEMI	45	45	53	.91	<.001
Unstable angina	55	55	47		<.0001
Medical history (%)					
Angina	62	69	66	<.01	.01
Bleeding	0.5	1.5	1.8	.02	.02
CHF	4.8	8.5	5.5	<.001	<.01
Diabetes	25	27	21	.30	.02
Hyperlipidemia	55	57	51	.21	.07
Hypertension	60	68	57	<.001	<.0001
MI	29	35	31	<.01	.02

Table 1 (*continued*)

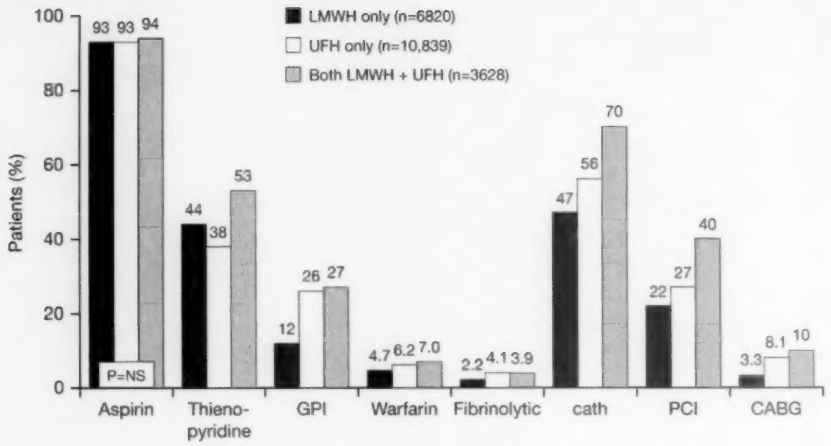
	LMWH only	UFH only	Both	*P*, LMWH vs UFH	*P* (3-way)
Medical history (%)					
PAD	8.5	11	11	.09	.08
Renal dysfunction†	4.9	8.9	8.5	<.001	<.001
Stroke	5.5	7.5	6.6	.07	.17
PCI	27	33	27	.01	.02
CABG	13	17	13	.03	.07
GRACE risk score*	116 (95, 137)	113 (93, 133)	117 (95, 143)	.04	.04
PCI with GP IIb/IIIa antagonists (n)	928	1091	730		
Demographics					
Age (y)*	64 (55, 73)	63 (54, 72)	63 (54, 72)	.06	.11
Male (%)	72	72	76	.97	.06
Weight (kg)*	76 (67, 86)	82 (72, 95)	78 (70, 89)	<.0001	<.0001
ACS diagnosis (%)					
NSTEMI	68	59	77	<.0001	<.0001
Unstable angina	32	41	23		<.0001
Medical history (%)					
Angina	45	60	55	<.0001	<.0001
Bleeding	0.5	1.5	1.8	.02	.02
CHF	4.8	11	5.9	<.0001	<.0001
Diabetes	24	28	25	.02	.05
Hyperlipidemia	55	62	52	.0005	<.0001
Hypertension	57	67	56	<.0001	<.0001
MI	21	34	28	<.0001	<.0001
PAD	7.0	11	9.3	<.01	.01
Renal dysfunction†	3.5	8.6	7.1	<.0001	<.0001
Stroke	5.2	7.8	6.5	.02	.07
PCI	18	33	23	<.0001	<.0001
CABG	12	23	14	<.0001	<.0001
GRACE risk score*	117 (99, 137)	111 (89, 134)	117 (95, 140)	.0122	<.0001
No PCI, GP IIb/IIIa antagonists (n)	390	617	231		
Demographics					
Age (y)*	67 (56, 75)	68 (57, 77)	67 (58, 75)	.21	.44
Male (%)	66	66	68	.97	.86
Weight (kg)*	78 (68, 88)	82 (70, 94)	80 (70, 90)	<.0001	<.001
ACS diagnosis (%)					
NSTEMI	77	69	86	.02	<.0001
Unstable angina	23	31	14		<.0001
Medical history (%)					
Angina	53	59	62	.07	.07
Bleeding	1.0	1.0	0.4	.94	.71
CHF	8.2	12	12	.08	.16
Diabetes	28	31	33	.35	.45
Hyperlipidemia	46	56	53	<.01	<.01
Hypertension	61	71	69	<.001	<.01
MI	28	34	28	.48	.07
PAD	11	13	12	.33	.60
Renal dysfunction†	5.1	7.5	9.6	.14	.11
Stroke	6.2	9.5	9.5	.06	.15
PCI	19	21	19	.13	.02
CABG	17	21	19	.13	.31
GRACE risk score*	127 (101, 156)	124 (99, 157)	126 (105, 157)	.5181	<.0001

CHF, congestive heart failure; *PAD*, peripheral arterial disease; *CABG*, coronary artery bypass graft surgery; *MI*, myocardial infarction; *PCI*, percutaneous coronary intervention.
*Median (interquartile range).
†Renal dysfunction defined as any documented history of renal compromise.

Within this cohort, patients given UFH alone had a greater likelihood of vascular disease and diabetes, whereas they had the lowest risk score for hospital death (Table I). Patients given LMWH alone were more likely than patients given UFH to receive thienopyridines (LMWH alone 86% vs UFH 77%) and less likely to receive warfarin (LMWH alone 3.1% vs UFH 5.4%) or a fibrinolytic drug (LMWH alone 1.9% vs UFH 4.6%) (all $P < .0001$).

Percutaneous coronary intervention and GP IIb/IIIa antagonists. Patients who underwent PCI

Figure 1



Inhospital pharmacologic medications and interventions in all patients. *cath*, Cardiac catheterization; *PCI*, percutaneous intervention; *CABG*, coronary artery bypass grafting; *GPI*, GP IIb/IIIa inhibition. *P* is less than .0001 for all 3-way comparisons unless otherwise stated.

and received GP IIb/IIIa antagonists were younger (63-64 years) and more likely to be male than the other groups, and they had a lower risk score than the overall cohort (117 vs 123) (Table I). Within this group, patients given UFH alone had more risk factors and comorbidities than the other groups, but they had a lower GRACE risk score (Table I). There were no significant differences in the use of oral antiplatelet therapies, warfarin, or fibrinolysis between these comparison groups. Most patients (92%) received a thienopyridine.

GP IIb/IIIa antagonists without PCI. The demographics of patients who received GP IIb/IIIa antagonists without PCI were similar to the overall population, but they had a high-risk score (126) (Table I). Within this cohort, patients with the lowest GRACE risk score received UFH. Patients given LMWH alone were more likely than those given UFH alone to receive thienopyridines (LMWH 51% vs UFH 29%, $P < .0001$); use of other therapies was comparable between groups.

Hospital mortality and bleeding events

Among the overall population with NSTE ACS, use of LMWH alone was associated with the lowest rates of hospital mortality and major bleeding (Table II). Among patients who did not receive GP IIb/IIIa antagonists or undergo PCI, the rates of mortality and major bleeding were lower in those who received LMWH alone than in those who received UFH alone (Table II); the difference in the mortality rate persisted after adjustment for baseline characteristics (Figure 2, *A*). Similarly, patients who underwent PCI and received an LMWH but not a GP IIb/IIIa antagonist had lower rates of mortality compared with their counterparts who were given UFH or both heparins (Table II); the difference persisted after multivariable adjustment (Figure 2, *A*). There was a trend toward an increase in major bleeding among patients receiving LMWH that reached significance after adjustment (Figure 2, *B*).

When GP IIb/IIIa antagonists were used in patients undergoing PCI, the associations between the type of heparin received and outcome differences became less pronounced. Mortality rates were similar, and there was a trend toward less bleeding in patients on LMWH; this was attenuated on multivariable analysis (Figure 2, *B*). Similarly, mortality rates were comparable among the medically managed patients receiving GP IIb/IIIa antagonists and either forms of heparin, and higher than those observed in the other groups (Table II). The rate of major bleeding in patients who received a GP IIb/IIIa antagonist and an LMWH but who did not undergo PCI during admission was higher than in those given UFH and GP IIb/IIIa antagonists after adjustment for baseline characteristics (Figure 2, *B*). Within this cohort, the rates of major bleeding in patients who received a GP IIb/IIIa antagonist and LMWH were higher in patients older than 75 years compared with younger patients (>75 years [n = 16] 14% vs ≤75 years [n = 10] 5%, $P \leq .001$). This observation was also true for patients given UFH (>75 years [n = 18] 8.3% vs ≤75 years [n = 12] 3.5%, $P < .01$).

Table II. Inhospital mortality and major bleeding rates

	LMWH only	UFH only	Both	*P*, LMWH vs UFH	*P* (3-way)
All patients (n)	10839	6820	3628		
Mortality (%)	2.7	4.1	2.9	<.0001	<.0001
Major bleeding (%)	1.8	2.7	2.8	<.0001	<.0001
No PCI, no GP IIb/IIIa antagonists					
Patients (n)	7957	4271	1919		
Mortality (%)	3.2	4.9	3.0	<.0001	<.0001
Major bleeding (%)	1.4	2.1	2.5	<.01	<.001
PCI without GP IIb/IIIa antagonists					
Patients (n)	1468	729	682		
Mortality (%)	1.0	2.9	1.6	<.001	<.01
Major bleeding (%)	2.2	1.8	2.4	.59	.76
PCI with GP IIb/IIIa antagonists					
Patients (n)	928	1091	730		
Mortality (%)	1.4	1.8	2.1	.53	.59
Major bleeding (%)	2.5	4.1	3.6	.05	.15
No PCI with GP IIb/IIIa antagonists					
Patients (n)	390	617	231		
Mortality (%)	3.6	3.4	8.7	.89	<.01
Major bleeding (%)	6.8	4.9	4.3	.22	.34

GP, glyco protein.

Hospital mortality and bleeding events in patients who received both heparin

After adjusting for baseline characteristics, compared with those given UFH alone, the risk of hospital mortality was lower in patients who did not receive either PCI or GP IIb/IIIa inhibitors but were given both heparins (Figures 3, *A*). Among these, bleeding was greater in patients treated with both heparins, but this difference was attenuated after adjustment (Figure 3, *B*). Patients who received GP IIb/IIIa inhibitors and UFH but did not undergo PCI had a lower mortality rate than their counterparts given both heparins (Figure 3, *A*), whereas the risk of major bleeding during hospitalization was not significantly different (Figure 3, *B*).

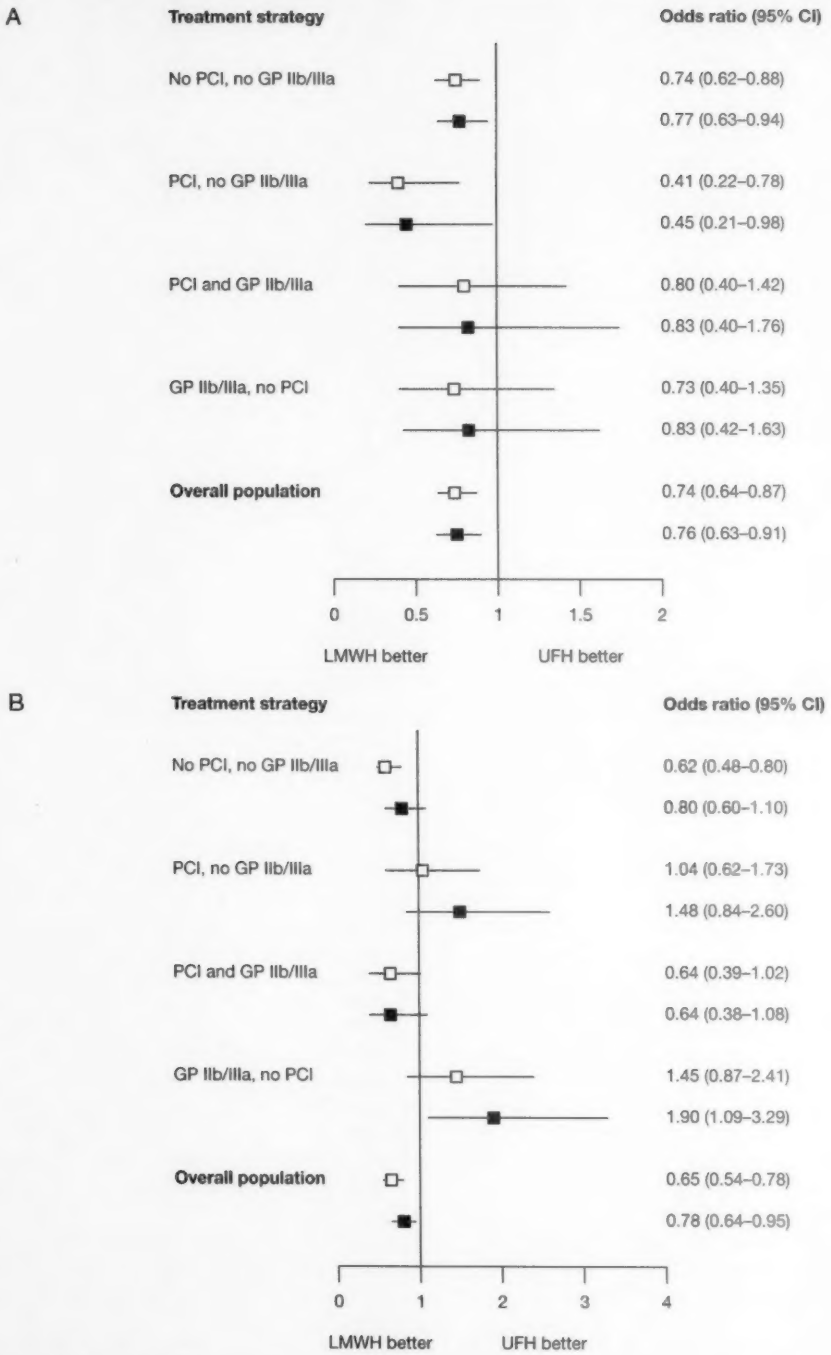
Discussion

Low molecular weight heparin is the preferred anticoagulant (in the absence of renal failure and provided that a coronary artery bypass graft is not planned within 24 hours) in both European and American (American College of Cardiology/American Heart Association) guidelines.[13] Recent trials,[7,8] conducted in high-risk populations with high rates of use of GP IIb/IIIa antagonist and coronary intervention, have not shown a significant improvement in outcomes but have shown some evidence of increased bleeding, especially when enoxaparin and UFH were given simultaneously. On a global scale, variations exist in the use of these therapies.[14] However, reports of their use in contemporary clinical practice do not reflect the increased bleeding rates observed in recent trials.[15,16] This finding suggests that real-world practices have evolved to capitalize on the clinical advantages of LMWH without adversely affecting patient outcomes.

In this analysis, approximately two thirds of the population were managed without PCI or intravenous GP IIb/IIIa antagonists. Thus, despite perceptions to the contrary,[7] in the real world, most patients follow a conservative management path, and treatment with LMWH is associated with low mortality rates and a slight increased risk of bleeding relative to UFH treatment.

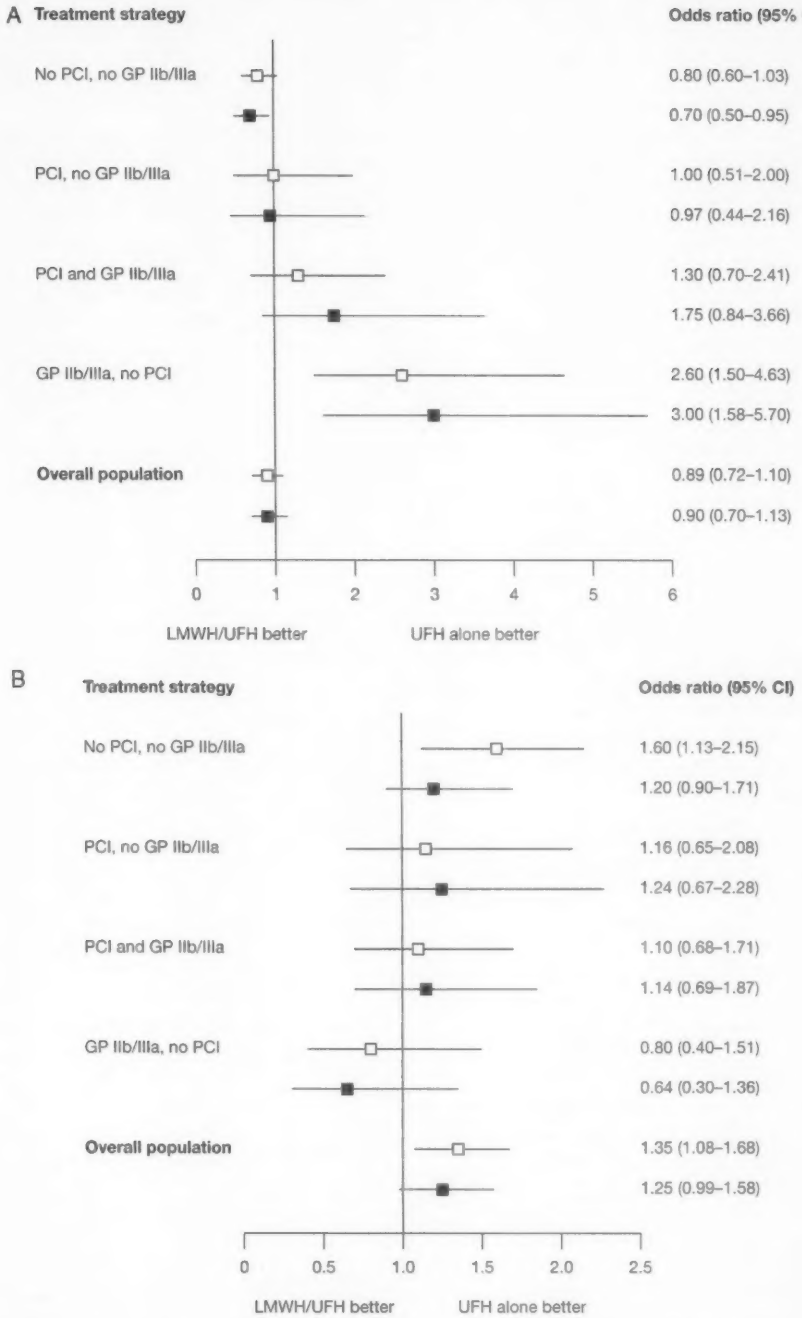
Overall, patients selected for PCI constituted a lower risk cohort than those managed medically. This likely reflected a previously reported risk-averse strategy to coronary intervention.[17] Among PCI patients who did not receive a GP IIb/IIIa antagonist, LMWH was used in patients with a higher GRACE risk score than those given UFH and was associated with lower mortality. A trend toward an excess of bleeding episodes, which became significant after multivariable analysis, was observed. This contrasts with data from a recent trial in stable patients undergoing elective PCI, which showed that an intravenous bolus of enoxaparin that generated comparable peak anti-Xa activity to that seen in patients with ACS after a subcutaneous injection caused less bleeding than UFH.[18] Similarly, in the recently reported PCI-ExTRACT-TIMI 25 study, patients with STEMI receiving fibrinolysis who went on to have a PCI had a lower risk of death or myocardial infarction and no excess in major bleeding if they received LMWH rather than UFH. Although these 2 trials enrolled different cohorts of patients from those assessed in our study, they both show that, in the contemporary era of interventional pharmacotherapy and intervention, use of LMWH does not increase bleeding in patients undergoing PCI. In reconciling our results with

Figure 2



Multivariable adjusted risk of (**A**) inhospital mortality and (**B**) major hemorrhage according to treatment strategy. *White box*, crude; *black box*, adjusted.

Figure 3



Multivariable adjusted risk of (**A**) inhospital mortality and (**B**) major hemorrhage in patients who received both low molecular weight heparin and UFH (referent, UFH alone). *White box*, crude; *black box*, adjusted.

those of these recent randomized clinical trials, it is noteworthy that, in PCI-ExTRACT-TIMI 25, the dose of enoxaparin was reduced in the elderly and in patients with renal impairment. Emerging data suggest that the dose of enoxaparin should be reduced when creatinine clearance is <50 mL/min.[19,20] A recent analysis from the CRUSADE initiative reported that patients with NSTE ACS in the community frequently receive excess doses of antithrombotic therapy.[21] These errors occur more often in vulnerable patients and predict an increased risk of major bleeding. Although we do not collect data on dosage of therapies in GRACE, it is likely that this observation is also true of our cohort and may have contributed to the excess bleeding seen in the PCI population receiving LMWH.

In the present analysis, among the subgroup of patients undergoing PCI who received a GP IIb/IIIa antagonist, mortality rates were low and comparable between LMWH and UFH groups. Similarly, bleeding rates were comparable regardless of the type of heparin used and were greater than in the absence of GP IIb/IIIa antagonists. Thus, despite current, safety-focused, interventional techniques, once an antithrombotic agent is combined with a GP IIb/IIIa antagonist, excess bleeding can be anticipated. Newer anticoagulant options, such as fondaparinux[22] and bivalirudin,[23] show some promise in reducing bleeding complications in the modern era of PCI. There will be opportunities to evaluate these newer therapies in the real-world setting in the GRACE study.

Patients managed medically with GP IIb/IIIa antagonists and either heparin constituted the highest risk cohort in this analysis. They consequently experienced the greatest mortality and risk of bleeding. These observations were most striking in patients older than 75 years and were true for both forms of heparin. Although bleeding was greater in patients receiving LMWH than UFH, the main trigger for excess bleeding in the medically managed elderly population is the addition of a GP IIb/IIIa antagonist.

The SYNERGY trial[7] focused attention on the negative impact of changing heparin treatment during the course of an ACS. Patients who crossed over therapies during this trial experienced an excess in bleeding events without any treatment benefit. Our analysis reinforces that observation. A higher proportion of patients receiving both forms of heparin underwent coronary angiography than was observed in patients receiving UFH or LMWH alone. This observation is likely to reflect the unease experienced by interventional cardiologists using LMWH in the catheterization laboratory, resulting in a tendency to change to UFH. Among patients undergoing PCI, however, mixing heparin treatments was associated with excess bleeding and no reduction in hospital mortality.

Based on the observations from this analysis, an initial strategy of LMWH started in the emergency department will be associated with low hospital mortality and bleeding risk in most patients who follow a conservative course. If coronary angiography is planned, LMWH should be continued—it is effective and associated with low event rates in the catheterization laboratory irrespective of whether a GP IIb/IIIa antagonist is used. The only group for whom LMWH should be initiated with caution is the elderly in whom GP IIb/IIIa antagonists are used in the context of medical management. In these patients, the risk of bleeding associated with effective anticoagulant and potent antiplatelet therapy is excessive.

Limitations

Our data provide a real-world insight into the management and outcomes of patients with ACS. Rather than the composite end points used in randomized trials, the size of our cohort allowed us to present data on mortality alone; although this is arguably the most important end point, failing to include myocardial infarction or target lesion revascularization in the analysis may have resulted in underrepresentation of the benefit of some therapies. Inhospital outcomes alone are reported and not long-term follow-up. Appropriate caution must be exercised in the interpretation of these results given the potential for residual confounding in these patients. Adjustment for known variables does not allow for unknown, or inadequately measured, factors to be balanced between comparison groups.

Conclusions

Low molecular weight heparin was associated with a reduced risk of death in most patients with NSTE ACS, irrespective of whether they were treated conservatively or invasively. Low molecular weight heparin was associated with lower mortality but with excessive bleeding episodes in patients undergoing PCI. Elderly patients managed medically with GP IIb/IIIa antagonists and either heparin were at particularly high risk of major bleeding.

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Sex-specific effects of diabetes on adverse outcomes after percutaneous coronary intervention: Trends over time

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Background Diabetes is a stronger risk factor for coronary heart disease in women than in men. Whether diabetes also poses greater risks to women after percutaneous coronary intervention (PCI) has not been examined.

Methods We examined 20 586 PCI procedures at Emory University Hospitals (Atlanta, GA) between 1990 and 2003. Hazard ratios (HRs) for 1-year major adverse cardiac events were calculated comparing diabetic with nondiabetic patients by sex and study year. Data were adjusted for demographic and clinical factors using Cox proportional hazards models.

Results Despite increasing patient age and comorbidity burden, diabetic and nondiabetic men had a significant improvement in PCI outcomes between 1990 and 2003 ($P < .001$). Diabetic women also tended to have improved PCI outcomes over time ($P = .073$), but not nondiabetic women ($P = .206$). Overall, diabetes had a stronger association with adverse outcomes in women (HR 1.93, 95% CI 1.55-2.40) than in men (HR 1.26, 95% CI 1.09-1.47) ($P = .002$ for the interaction between sex and diabetes). The excess risk associated with diabetes in women, however, was largely driven by early study years (1990-1993). This excess risk associated with diabetes in women declined over time, and diabetes had a similar effect on outcomes in both women and men in more recent years ($P = .010$ for the interaction between sex, diabetes, and time).

Conclusions Percutaneous coronary intervention outcomes of diabetic and nondiabetic men have improved in recent years. However, among women, diabetic patients had greater improvements in outcomes after PCI compared with nondiabetic patients. As a result, diabetes is no longer a stronger risk factor for adverse outcomes after PCI in women than in men. (Am Heart J 2007;153:970-8.)

Although coronary heart disease (CHD) has remained the leading cause of death in the United States for the last 50 years, significant improvements in CHD mortality have occurred since 1980, mostly attributed to better therapy for CHD and CHD risk factors.[1-6] These improvements, however, are larger in men than in women.[2] A possible reason for this discrepancy is that women with CHD may derive less benefit from new and common treatments for CHD than men.

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Percutaneous coronary intervention (PCI) is a common cardiovascular procedure with >1 million PCI procedures performed in the United States annually, 33% in women.[7,8] Percutaneous coronary intervention in women improves anginal symptoms and quality of life,[9] and women have had better outcomes after PCI in recent years.[8,10] However, women continue to have higher rates of complications after PCI compared with men, including contrast-induced nephropathy, bleeding, stroke, and vascular complications.[8,11-16]

Although the reasons for these sex-related outcome differences after PCI are not known, it is possible that they are modulated by diabetes. Diabetes is more prevalent in women than in men with CHD.[17] Among patients without established CHD, diabetes is also a stronger risk factor for adverse cardiovascular outcomes in women than in men.[18-20] This sex-diabetes interaction has also been documented for congestive heart failure (CHF),[21] and stroke.[22] However, whether diabetes poses greater risks to women than to men with established CHD after PCI is not clear. In addition, whether this

Table I. Demographic and clinical characteristics of the entire patient population according to diabetes status and sex

	Diabetic patients (N = 4625)		Nondiabetic patients (N = 15961)	
Characteristic	**Women (n = 1743)**	**Men (n = 2882)**	**Women (n = 4474)**	**Men (n = 11487)**
Mean age	64 ± 11	62 ± 10	65 ± 19	61 ± 11
White (%)	80*	88*	90*	93*
Tobacco (%)	14	16	23*	25*
Heart failure (%)	15*	11*	8*	5*
Hypertension (%)	80*	70*	63*	51*
Prior MI (%)	39*	46*	38*	44*
Prior PCI (%)	19*	23*	15*	19*
Prior CABG (%)	19*	32*	13*	21*
Elective PCI (%)	92	93	90*	91*
EF				
Missing	25*	23*	22*	20*
EF <40	7*	10*	5*	7*
EF ≥40	67*	66*	72*	73*
Stent	41	42	41*	38*
Plavix	19	19	19*	17**
Gp2B3A inhibitor	13	14	12	14

EF, Ejection fraction; *GP2B3A*, glycoprotein IIb/IIIa.
*$P \leq .05$ for comparison between women and men by diabetes status. For all other comparison, $P \geq .05$.

adverse effect of diabetes has decreased in recent years, with improved medical therapy and PCI treatments, is unknown. The purpose of this study was to evaluate whether diabetes is associated with more adverse outcomes after PCI in women than in men and whether this relationship has changed over a recent 14-year period.

Methods

Study population and design

We evaluated 20586 PCI procedures performed at Emory University Hospitals (Atlanta, GA) from January 1990 to December 2003. Data were drawn from the Emory Cardiac Database, a registry of cardiac procedures at Emory University.[23,24] At the time of PCI, trained house staff physicians prospectively collected information on cardiovascular risk factors, medical history, current medical therapies, catheterization and procedural data, postprocedure hospital course, periprocedural medications, and discharge medications. Subjects were followed up to 1 year.

Participants were classified as diabetic if they had a history of diabetes documented by a house staff physician. Periprocedural medication data were available from 2000 to 2003. In this subgroup of patients, we examine the agreement between our definition of diabetes, based on chart documentation, with a more rigorous definition based on the patient receiving any oral diabetic medication or insulin therapy during the periprocedural hospitalization. We found that 85% of patients between 2000 and 2003 with our study definition of diabetes received medications (oral or insulin) to treat hyperglycemia, showing excellent correspondence between our study definition of diabetes and medically treated diabetes. The remaining small percentage (15%) of patients who were not taking medication for diabetes may include milder forms, diet-controlled diabetes cases. Laboratory data were not available for this cohort; therefore, correlation of our study definition of diabetes with fasting blood glucose was not possible.

History of CHF was defined as any symptoms consistent with New York Heart Association class ≥2 CHF. Patients were determined to have hypertension, prior myocardial infarction (MI), prior PCI, and prior coronary artery bypass graft (CABG) surgery if there was a history of these comorbidities documented by a house staff physician.

Study end point

The study end point was a composite end point of major adverse cardiac events (MACE) at 1 year, defined as death, nonfatal MI, and myocardial revascularization (CABG, target lesion revascularization, or PCI for a new lesion). As a secondary end point, we examined death or MI. Our goal was to evaluate trends in outcomes over time given improvements in medical therapy (greater use of angiotensin-converting enzyme inhibitors, β-blockers, and statins) and PCI technology (stents). Given that >50% of revascularization procedures among diabetic patients are for new lesions and disease progression rather than restenosis,[25] revascularization at large rather than target lesion revascularization was chosen as the end point. All patients were contacted by phone at 1 year after discharge using a standardized questionnaire and were asked about new hospital admissions, repeat revascularization, and other cardiac procedures and health problems. Death was determined by review of the state death index.

Data analysis

We first compared baseline characteristics by sex and diabetes status using the t test for continuous variables and the χ^2 for categorical variables. Trends in overall event rates were tested using the Mantel-Haenszel test.

We then divided the 14-year period into 7 time groups: time group 1, 1990-1991; time group 2, 1992-1993; time group 3, 1994-1995; time group 4, 1996-1997; time group 5, 1998-1999; time group 6, 2000-2001; and time group 7, 2002-2003. In each period, we compared demographic and clinical data between diabetic patients and nondiabetic patients for both men and women. Differences in the trends of patient characteristics and therapies over time were assessed with the Mantel-Haenszel test for all binomial variables and with analysis of variance for continuous variables. Multivariable analysis was conducted using Cox proportional hazards models. Seven Cox models were fitted, 1 for each time group. From these models, we calculated HRs for 1-year MACE comparing diabetic to nondiabetic patients by sex and evaluated the significance of the sex-diabetes interaction. Hazard ratios and 95% CIs for each combination of sex and diabetes status were calculated using contrast terms in the regression procedure. To test for changes in the sex-specific effects of diabetes over time, we included a 3-way interaction term between diabetes, sex, and time group in a Cox model fitted using the pooled 14-year sample before and after adjusting for the same covariates, as in the previous 7 models. All 2-way interactions were included in the 14-year sample models, and interaction terms were tested for significance with the Wald test. Time group was treated as an ordinal variable.

To assess the impact of baseline demographics and comorbidities on the sex-specific effects of diabetes over time, 3 consecutive models for each time group and the pooled 14-year sample were constructed. Model 1 adjusted for age and race. Model 2 further adjusted for smoking, CHF, hypertension, prior MI, prior revascularization, ejection fraction, and elective PCI status. Model 3 adjusted for the use of coronary stent at the time of PCI.

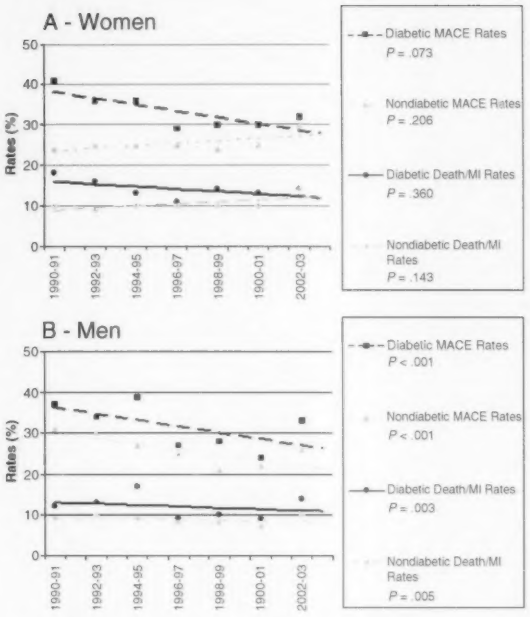
Given the large number of subgroups necessary to study trends over time, we conducted a secondary analysis, with only 2 time points as opposed to 7 periods, to examine whether similar findings would be obtained with a larger sample size per group. We divided the 14-year period into pre-stent (1990-1995) and post-stent (1996-2003) groups. Multivariable analysis was conducted using the Cox proportional hazards models as outlined above. All analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC).

Results

Sample characteristics and overall MACE-free survival

In the entire sample, women were more likely to be diabetic than men (28% vs 20%, $P < .001$). Women were older than men in both the diabetic (64 vs 62, $P < .001$) and the nondiabetic populations (66 vs 61, $P < .001$). Diabetic patients of both sexes were less likely to be white and to smoke but more likely to have CHF, hypertension, and low ejection fraction (Table I). All groups showed a worsening profile in more recent years, with similar trends over time. In all groups, patients were older and more likely to be African American, to have heart failure, hypertension, and be admitted for a nonelective PCI in recent years. However, the prevalence of prior MI decreased over time (Appendix Tables 1 and 2).

Figure 1



Trends in unadjusted MACE and death/MI rates after PCI by sex and diabetes status between 1990 and 2003. **Panel A,** Trends over time for women. **Panel B,** Trends over time for men. P indicates significance of trend over time.

In the entire study period, there were 5682 (28%) MACE. Given that the population consisted largely of elective PCI patients, the number of deaths and MI events was small. There were 970 (5%) deaths, 1136 (6%) MI events, 1367 (7%) CABG procedures, and 3357 (16%) repeat PCI.

In the entire sample, there was no difference in MACE between women and men (HR 1.03, 95% CI 0.97-1.09). However, diabetes was associated with a 28% higher risk of MACE (95% CI 20%-36%). This association with adverse outcomes was greater in women (HR 1.93, 95% CI 1.55-2.40) than in men (HR 1.26, 95% CI 1.09-1.47), with a significant interaction between sex and diabetes ($P = .002$).

Trends over time

Rates of MACE showed improvement in all groups over time, except for nondiabetic women (Figure 1). Overall similar trends were seen when death or MI were

Table II. Unadjusted and adjusted HR for diabetes versus nondiabetes by sex for each time group

	1990-1991	1992-1993	1994-1995	1996-1997	1998-1999	2000-2001	2002-2003	Overall 1990-2003	P*
Unadjusted model									
Female	1.90 (1.49-2.42)	1.53 (1.18-1.99)	1.47 (1.13-1.92)	1.21 (0.92-1.60)	1.32 (1.02-1.71)	1.25 (0.95-1.63)	1.06 (0.79-1.42)	1.93 (1.55-2.40)	.010
Male	1.26 (1.07-1.48)	1.15 (0.95-1.39)	1.56 (1.29-1.89)	1.10 (0.88-1.37)	1.36 (1.11-1.67)	1.09 (0.87-1.36)	1.30 (1.04-1.62)	1.26 (1.09-1.47)	
P for interaction (sex-DM)	.006	.083	.716	.580	.863	.447	.276	.002	
Model 1									
Female	1.91 (1.50-2.43)	1.55 (1.19-2.02)	1.47 (1.13-1.93)	1.21 (0.91-1.59)	1.30 (1.01-1.69)	1.25 (0.95-1.64)	1.08 (0.81-1.45)	1.94 (1.56-2.43)	.009
Male	1.25 (1.07-1.47)	1.16 (0.96-1.39)	1.55 (1.28-1.88)	1.09 (0.87-1.36)	1.34 (1.10-1.65)	1.09 (0.88-1.36)	1.31 (1.05-1.64)	1.27 (1.09-1.48)	
P for interaction (sex-DM)	.004	.074	.767	.567	.866	.464	.309	.002	
Model 2									
Female	1.98 (1.53-2.55)	1.42 (1.07-1.90)	1.56 (1.18-2.07)	1.10 (0.81-1.48)	1.31 (0.97-1.76)	1.23 (0.89-1.70)	1.23 (0.86-1.76)	1.83 (1.44-2.31)	.059
Male	1.21 (1.02-1.44)	1.06 (0.86-1.29)	1.50 (1.23-1.83)	1.05 (0.84-1.33)	1.37 (1.09-1.72)	0.97 (0.75-1.26)	1.28 (0.98-1.68)	1.19 (1.01-1.41)	
P for interaction (sex-DM)	.002	.090	.807	.834	.815	.257	.853	.004	
Model 3									
Female	1.97 (1.53-2.55)	1.42 (1.07-1.90)	1.56 (1.18-2.07)	1.08 (0.80-1.45)	1.31 (0.97-1.76)	1.24 (0.90-1.71)	1.23 (0.86-1.76)	1.83 (1.44-2.31)	.058
Male	1.22 (1.02-1.44)	1.06 (0.86-1.29)	1.50 (1.22-1.83)	1.06 (0.84-1.34)	1.37 (1.09-1.72)	0.98 (0.76-1.26)	1.28 (0.98-1.68)	1.20 (1.02-1.41)	
P for interaction (sex-DM)	.002	.090	.808	.940	.815	.252	.864	.004	

Model 1 adjusts for age and race. Model 2 adjusts for all factors in model 1 plus tobacco use, CHF, hypertension, prior MI, prior PCI, prior CABG, elective PCI status, and EF. Model 3 adjusts for all factors in model 2 plus the use of coronary stent. *DM*, Diabetes mellitus.
*Indicates whether there is a significant difference in the sex, diabetes, and time interaction in the pooled 14-year sample.

examined separately from revascularization, although the power to examine this end point was lower.

Table III shows the crude and adjusted HRs and 95% CIs for 1-year MACE associated with diabetes for women and men in each time group. In the initial time group, 1990-1991, diabetes was associated with almost a 2-fold greater MACE rate in women (HR 1.90, 95% CI 1.49-2.42) but a much smaller effect in men (HR 1.26, 95% CI 1.07-1.48), with a significant interaction between sex and diabetes ($P = .006$) (Table II). The excess risk associated with diabetes in women was less in the subsequent time groups, and by 1994-1995 women and men with diabetes had equivalent outcomes. The 3-way interaction between sex, diabetes, and time was significant in the unadjusted model ($P = .010$), and there was a trend toward significance in the multivariable adjusted models ($P = .058$), indicating a significant decrease over time in the excess risk associated with diabetes comparing women with men. These results were driven by the fact that MACE rate decreased over time in all groups except in that of nondiabetic women (Figure 1). Adjusting for demographic factors, comorbidities, and the use of coronary stents did not significantly change the results (Table II). Further adjusting for the use of plavix and glycoprotein IIb/IIIa inhibitors also did not materially change the study estimates (data not shown).

Pre-stent versus post-stent

When only 2 time points were considered, pre-stent (1990-1995) versus post-stent (1996-2003), similar results were obtained. In the pre-stent era, diabetic women had a 63% higher risk for adverse events in the first year after PCI compared with nondiabetic women. In contrast, diabetic men only had a 30% higher risk compared with nondiabetic men in the same period ($P = .013$ for sex-diabetes interaction). In the post-stent era,

Table III. Unadjusted and adjusted HR for diabetes versus nondiabetes by sex in the pre-stent and post-stent era

	Pre-stent era			Post-stent era		
	HR	**95% CI**	***P****	**HR**	**95% CI**	***P****
	Diabetes vs nondiabetes			**Diabetes vs nondiabetes**		
Crude						
Women	1.63	1.41-1.89	.013	1.21	1.06-1.39	.966
Men	1.30	1.17-1.44		1.21	1.08-1.34	
Model 1						
Women	1.64	1.42-1.91	.01	1.21	1.05-1.39	.984
Men	1.30	1.17-1.44		1.20	1.08-1.34	
Model 2						
Women	1.64	1.40-1.93	.003	1.24	1.06-1.45	.493
Men	1.24	1.11-1.38		1.15	1.02-1.30	
Model 3						
Women	1.64	1.40-1.92	.003	1.23	1.05-1.44	.516
Men	1.24	1.11-1.38		1.15	1.02-1.30	

Model 1 adjusts for age and race. Model 2 adjusts for all factors in model 1 plus tobacco use, CHF, hypertension, prior MI, prior PCI, prior CABG, elective PCI status, and EF. Model 3 adjusts for all factors in model 2 plus the use of coronary stent.
*Indicates whether there is a significant sex-diabetes interaction.

however, diabetes was associated with a 21% increased risk of 1-year MACE for both men and women. ($P = .966$ for sex-diabetes interaction) (Table III).

Discussion

Among patients with established CHD undergoing PCI, we found that diabetes is associated with more adverse outcomes in women than in men. However, the overall stronger effect of diabetes among women was driven by early years, 1990-1993. We also found that there was a significant change in the sex-diabetes relationship over time. Among men, diabetic and nondiabetic patients had equivalent improvements in MACE-free survival after PCI. Among women, however, diabetic patients had greater improvements in PCI outcomes relative to nondiabetic patients. These trends resulted in a significant decline in the excess risk associated with diabetes in women.

Diabetes is associated with a greater risk for CHD in women than in men.[19,20,26] However, among patients with established coronary artery disease, in general, diabetic women were reported to have only a slight increased risk of death compared with diabetic men.[27,28] In our study, we found that the relative effect of diabetes on PCI outcomes was greater among women than among men only in early study years. Therefore, although diabetes remains a major risk factor for cardiovascular events after PCI, the adverse effect of diabetes in patients with established CHD is equivalent for women and men in recent years. This equivalent risk among diabetic men and women in current times is consistent with recent studies examining sex differences in PCI outcomes among diabetic patients or in the prognostic importance of diabetes in modern cohorts.[28,29]

A possible reason for the adverse association between diabetes and PCI outcomes is the older age of diabetic patients and their higher burden of other CHD risk factors. However, unlike other studies,[19,30] the association between diabetes and outcomes in our study did not change significantly after adjusting for baseline demographics, comorbidities, and the use of primary coronary stenting. Differences in study end points may be one reason why the adverse effect of diabetes for both women and men did not diminish in multivariable analysis in our study as it did in previous investigations. In our study, revascularization was the major component of the primary outcome, whereas most other studies have examined mortality as the primary outcome. Diabetic patients are more likely to have repeat revascularization after an initial PCI procedure in both the target lesion and in nontarget lesions.[25,31-33] Many mechanisms such as excessive neointimal reaction, increased vascular sympathetic tone secondary to exogenous insulin, and smaller target vessels in diabetic patients have been proposed to explain their higher rate of repeat revascularization, which may not be altered by coexisting comorbidities.[29,34-37] Consideration of coronary stenting in our analysis also did not change the association between diabetes and MACE. This result, however, is not surprising because a number of repeat revascularization procedures in patients with diabetes is due to disease progression in nontarget lesions.[25]

We found that despite their older age and higher prevalence of comorbidities, the outcomes of diabetic patients undergoing PCI, both women and men, have dramatically improved in recent years. A comparison of

CHD mortality rates between 2 representative US cohorts, one in 1971-1975 and the other in 1982-1984, showed decreasing CHD mortality rates for diabetic men but increasing CHD mortality for diabetic women.[38] More recent data from the Worcester Heart Attack Study, however, demonstrated an improvement over time for both women and men with diabetes and acute MI.[27] Our data are consistent with the notion that outcomes for diabetic patients with CHD are improving in recent years for both men and women.

A concerning and surprising finding of our study is that nondiabetic women did not show improvements in outcomes over time consistent with the other groups. One possible explanation is confounding due to improved medical therapies such as angiotensin-converting enzyme inhibitors and statins. It is accepted that men and diabetic patients have a greater atherosclerotic burden compared with women and nondiabetic patients. Therefore, perhaps nondiabetic women had minimal or focal disease, whereas diabetic women and men had more diffuse disease. Improvements in medical therapy that modify disease progression would have greatest benefit in those groups with more diffuse disease, that is, men and diabetic women.[39] Another possibility is that the risk profile of diabetic women improved over time, perhaps because of changes in referral. However, this is unlikely because similar trends for comorbidity prevalence over time were noted in each subgroup. Therefore, differential referral patterns by diabetes or sex over time should not be an explanation for our results. Another factor that may potentially affect our trends is the change in the accepted diagnostic criteria for diabetes, with lower cut points recommended in year 1997.[40] However, this change would be expected to affect men and women in a similar fashion. Furthermore, it is unlikely that the new diabetes diagnostic criteria would affect the association of diabetes with CHD.[41]

A limitation of our study is its relatively small sample size in some of the sex-time subgroups. Although we studied >20000 patients, the cohort was divided into many subgroups for analysis. However, in each subgroup we had ≥65 outcome events, so it is unlikely that our models were overfitted. Also, when we only examined 2 periods, each including a much larger sample size, conclusions were similar. Thus, low power should not be a concern in our findings. Diabetic patients were those with diagnosed or treated diabetes. Unfortunately, data on fasting blood glucose were not available to us; thus, undiagnosed diabetic patients may have been misclassified as nondiabetic patients. This, however, would falsely increase the risk in the nondiabetic group and bias the results toward the null. Another possible limitation is the lack of information on diabetes duration, treatment, or control. For example, insulin requirement may differ between diabetic women and men and may influence PCI outcomes.[29,34,42] Finally, given that most patients in this study had elective PCI, the number of hard end points, death, and MI was relatively small.

In conclusion, the outcomes after PCI improved substantially over the last 14 years in diabetic patients (women and men) and nondiabetic men. Nondiabetic women have not shown similar positive changes over time. As a result, in recent years diabetes is no longer associated with more adverse outcomes after PCI in women than in men.

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Appendix A

Table 1. Demographic and clinical characteristics of female patients according to diabetes status and time group

	1990-1991		1992-1993		1994-1995		1996-1997		1998-1999		2000-2001		2002-2003			
Characteristic	**Non-DM N = 815**	**DM N = 244**	**Non-DM N = 616**	**DM N = 245**	**Non-DM N = 596**	**DM N = 242**	**Non-DM N = 628**	**DM N = 257**	**Non-DM N = 658**	**DM N = 296**	**Non-DM N = 651**	**DM N = 255**	**Non-DM N = 510**	**DM N = 204**	**Non-DM *P****	**DM *P****
Mean age	59	63	61	63	60	65	60	63	62	64	61	61	62	64	.009	.442
White (%)	95	89	96	85	94	83	93	77	90	74	90	71	87	71	<.001	<.001
Tobacco (%)	20	14	21	12	24	14	23	15	23	14	26	16	24	14	.168	.931
Heart failure (%)	7	13	7	14	8	18	6	16	11	14	7	14	8	19	.021	.664
Hypertension (%)	57	70	58	75	55	81	65	82	66	80	69	84	78	92	<.001	<.001
Prior MI (%)	40	45	45	44	47	47	42	39	35	40	32	35	24	25	<.001	<.001
Prior PCI (%)	19	23	16	16	12	17	14	17	14	19	13	21	19	21	.002	.376
Prior CABG (%)	14	20	15	17	13	18	11	21	11	22	12	23	12	14	.310	.229
Elective PCI (%)	92	93	94	94	92	95	91	90	87	92	85	92	83	88	<.001	.132
EF																
Missing (%)	12	9	8	10	9	12	21	24	27	30	37	44	41	50	<.001	<.001
EF <40 (%)	7	8	7	9	6	6	7	6	7	8	7	5	9	8	.289	.561
EF ≥40 (%)	81	83	85	81	85	82	72	70	66	62	56	50	50	42	<.001	<.001
Stent	2	2	4	3	5	7	42	37	73	70	87	81	85	87	<.001	<.001
Plavix	0	0	0	0	0	0	0	0	31	27	52	52	58	57	<.001	<.001
Gp2B3A inhibitor	0	0	0	0	0	0	3	4	28	27	37	33	22	28	<.001	<.001
PCI lesion																
Length (mm)	5.8	6.2	6.9	7.2	8.4	8.4	10.5	10.1	12.0	11.7	10.3	11.5	12.5	13.2	<.001	<.001
Type																
A	11	10	9	9	10	12	13	7	11	14	16	10	14	10	.057	.112
B	31	33	37	36	32	35	30	29	32	32	32	33	36	36	.199	.288
B2	41	37	35	34	38	36	38	58	39	38	35	41	33	39	.011	.714
C	17	20	19	21	20	17	19	6	18	16	17	16	17	15	.924	.644

*Indicates whether there is a significant trend over time for factors among nondiabetic and diabetic women.

Appendix B

Table 2. Demographic and clinical characteristics of male patients according to diabetes status and time group

	1990-1991		1992-1993		1994-1995		1996-1997		1998-1999		2000-2001		2002-2003			
Characteristic	**Non-DM N = 2366**	**DM N = 514**	**Non-DM N = 1865**	**DM N = 409**	**Non-DM N = 1612**	**DM N = 357**	**Non-DM N = 1532**	**DM N = 371**	**Non-DM N = 1602**	**DM N = 456**	**Non-DM N = 1460**	**DM N = 435**	**Non-DM N = 1050**	**DM N = 340**	**Non-DM *P****	**DM *P****
Mean age	59	60	61	63	60	62	60	61	62	63	61	63	62	64	<.001	<.001
White (%)	95	90	96	91	94	89	93	86	90	88	90	86	87	84	<.001	.044
Tobacco (%)	24	20	22	14	23	17	28	19	24	14	27	14	24	13	.001	.023
Heart failure (%)	3	8	4	11	5	11	4	10	5	10	6	12	5	12	.005	.493
Hypertension (%)	45	60	44	62	48	65	51	71	56	73	59	79	65	82	<.001	.002
Prior MI (%)	47	49	46	46	49	50	50	47	40	47	36	41	30	37	<.001	<.001
Prior PCI (%)	22	26	18	21	19	20	17	21	19	24	19	21	20	26	.002	.141
Prior CABG (%)	21	28	24	38	22	32	19	30	19	31	21	29	21	34	.011	.050
Elective PCI (%)	94	94	94	96	93	93	91	94	89	92	87	93	81	89	<.001	.008
EF																
Missing (%)	12	11	8	11	9	11	21	19	27	30	37	42	41	44	<.001	<.001
EF <40 (%)	7	9	7	16	6	12	7	12	7	8	7	8	9	6	.072	<.001
EF ≥40 (%)	81	81	85	73	85	76	72	67	66	62	56	51	50	50	<.001	<.001
Stent	3	2	4	3	8	11	41	41	77	71	86	83	90	88	<.001	<.001
Plavix	0	0	0	0	0	0	0	0	30	26	58	56	60	57	<.001	<.001
Gp2B3A inhibitor	0	0	0	0	0	0	5	5	33	27	41	42	30	27	<.001	<.001
PCI lesion																
Length (mm)	6.4	6.0	7.4	7.4	9.1	9.1	10.8	12.0	13.0	13.4	11.8	11.7	13.3	13.3	<.001	<.001
Type																
A	11	11	15	11	11	14	12	11	11	11	10	12	10	10	.539	.902
B	35	34	32	33	32	32	35	33	30	33	32	35	36	36	.169	.450
B2	36	36	36	41	39	38	42	36	42	36	38	36	35	33	.001	.342
C	18	20	17	16	18	16	17	20	17	20	20	17	19	21	.115	.738

*Indicates whether there is a significant trend over time for factors among nondiabetic and diabetic men.

Randomized comparison of dexamethasone-eluting stents with bare metal stent implantation in patients with acute coronary syndrome: Serial angiographic and sonographic analysis

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Aims The aim of this study is to compare the anti-inflammatory effect of the dexamethasone preloaded stent (Dexamet, Abbott, Galway, Ireland) with the bare metal stent (BMS; BiodivYsio, Biocompatibles Cardiovascular LTD, Galway, Ireland) in patients with acute coronary syndrome (ACS) assessed by angiographic (QCA) and intracoronary ultrasound (ICUS).

Methods and Results One hundred twenty patients with ACS were randomly assigned to revascularization using the Dexamet stent (n = 60) or BMS (n = 60). Serial QCA analysis and ICUS analysis were performed during long-term follow-up (2.9 F; 20 MHz transducer; Volcano Corp, Brussels, Belgium). Power calculations were performed for QCA-derived differences of lumen loss. In addition, statistical analysis was performed (SPSS for Windows 12.0.1). The target lesion revascularization rate was lower in the Dexamet group (10 [16.67%] vs 20 [33.33%] patients; $P = .031$). The QCA revealed improved lumen restoration in the Dexamet stent group (lumen loss, 0.55 ± 0.65 vs 1.07 ± 0.92 mm [$P = .001$]; loss index, 0.20 ± 0.23 vs 0.46 ± 0.42 [$P < .001$]). The ICUS revealed greater neointimal proliferation in the BMS versus the Dexamet stent group (3.36 ± 1.03 vs 3.05 ± 1.38 mm^2; $P < .001$). Death (n = 1) and the number of total occlusions of the stent segment (n = 1) were identical in both groups.

Conclusion Dexamet stents, in comparison with the BMS stents, reduced the target lesion revascularization rate in patients with ACS and lead to better lumen restoration during long-term follow-up.
(Am Heart J 2007;153:979.e1-979.e8.)

Secondary prevention outcomes among black and white cardiac rehabilitation patients

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Background Disparities in coronary heart disease and related risk factors persist. It is unknown if cardiac rehabilitation (CR) narrows the gap in risk factor control between Black and White patients. Thus, we compared baseline characteristics and secondary prevention outcomes between black and white CR patients.

Methods Data from patient records (n = 616, mean age 62 ± 10 years, 29% women, 25% black) collected between January 1996 and June 2006 were examined. Comparisons were made between Blacks and Whites for baseline characteristics, changes in secondary prevention measures during CR, and the proportion of patients at treatment goals before and after CR. General linear regression modeling was used to determine the effect of race/ethnicity on outcomes.

Results At baseline, Blacks had more hypertension and diabetes and more adverse measures for blood pressure, low-density lipoprotein and non–high-density lipoprotein cholesterol (non-HDL-C), hemoglobin A_{1c}, 6-minute walk distance, and Short-Form Health Survey (SF-36) physical component score. At CR completion, improvement ($P < .05$) was achieved among whites in all measures except for HDL-C and systolic blood pressure. Among Blacks, improvement did not reach significance for HDL-C, body mass index, waist circumference, and hemoglobin A_{1c} (when diabetes was present). When adjusting for age, gender, number of sessions attended, and baseline measure, Whites improved more than Blacks in 6-minute walk distance, self-reported physical activity, body mass index, waist circumference, low-density lipoprotein cholesterol, and hemoglobin A_{1c} (all $P < .05$).

Conclusion Blacks entered CR with more adverse risk factor measures compared with Whites. Although both groups gained secondary prevention benefits, the degree of improvement was less for Blacks than Whites, and this was especially evident among black women. (Am Heart J 2007;153:980-6.)

Reducing widespread health disparities in cardiovascular disease is a major public health and clinical challenge.[1,2] Among Blacks, coronary heart disease (CHD) is the most important cause of death and, compared with other racial/ethnic groups, contributes to a higher CHD mortality.[3] Differences in CHD outcomes between black and white patients have been attributed to patient-related factors (socioeconomic, education, marital status, geographic location, and delays in seeking care),[4] self-reported and measured risk factors,[1,3,5] and treatment-related factors such as lower use of reperfusion therapies,[6-8] invasive coronary interventions,[4,9] and appropriate pharmacotherapy.[9]

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Although short-term survival rates after acute coronary events are similar between black and white patients,[9-11] Blacks have poorer longer-term outcomes, such as higher 5-year mortality rates[10] and report more angina, worse quality of life, and lower physical functioning at 1 year after an acute coronary syndrome.[11] Despite extensive evidence documenting the importance of lifestyle factors in the management of cardiac risk factors, little progress has been made in reducing physical inactivity and poor nutrition, especially among Blacks.[1]

The recent American Heart Association (AHA)/American College of Cardiology (ACC) guidelines for secondary prevention for patients with coronary and other atherosclerotic disease recommend referral of patients with CHD to a medically supervised program for exercise and risk factor modification, such as cardiac rehabilitation (CR).[12] Cardiac rehabilitation is associated with improvements in exercise capacity, lipid profiles, body mass index (BMI), psychosocial well-being, and quality of life, as well as reduction in hospitalization costs and lower rates of fatal myocardial infarction, cardiac mortality, and all-cause mortality.[13] However, limited data are available in CR populations that include adequate representation of diverse racial/ethnic groups

to explore for differences in outcomes related to comprehensive secondary prevention therapies.

The purpose of this study was to compare baseline characteristics and secondary prevention outcomes between black and white patients and determine the effect of race/ethnicity on improvement in risk factor control among patients completing a CR program.

Methods

The data for this study were collected from a CR/secondary prevention program in an academic medical center. A case manager (registered nurse or exercise physiologist) performed initial and follow-up patient assessments. Cardiac rehabilitation sessions included a combination of telemetry-monitored exercise, individual counseling, and group education classes. A typical program involved 24 to 36 sessions, 2 to 3 times per week and completed within 3 to 4 months. Informed consent was obtained from patients at CR enrollment for use of individual data for clinical purposes and aggregate patient data for quality improvement and research purposes. The current study was approved by the academic medical center's institutional review board.

Patient data were entered into the CR database at the time of program enrollment and completion. Race/ethnicity was classified in the medical record based on the patient's self-report. Risk factors were assessed and classified as follows: (1) diabetes, hypertension, and dyslipidemia based on physician documentation; (2) smoking based on self-reported tobacco use within the last 6 months; (3) obesity defined as BMI $\geq$30 kg/m^2; and (4) low physical activity pattern (<30 minutes of moderate intensity activity 5 days per week or <20 minutes of vigorous activity 3 days per week) during the 6 months before referral. Submaximal functional capacity was assessed by the 6-minute walk test.[14] Patients were classified into low, intermediate, or high clinical risk categories according to criteria from the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR).[15] A comorbidity index was calculated as previously published,[16] and depression screening was assessed with the Beck Depression Inventory II. Current physical activity behavior was assessed by self-reported minutes per week (at least 10 minutes duration) engaged in moderate and/or vigorous activities during the past week and expressed in metabolic equivalent hours (METhrs). Diet was assessed with the MEDFICTS (Meats, Eggs, Dairy, Fried foods, In baked goods, Convenience foods, Table fats, Snacks) questionnaire with a score <40 indicating dietary patterns in accordance with the AHA dietary recommendations.[17] Perceived health status was assessed with the Medical Outcomes Study Short-Form Health Survey (SF-36), and the physical and mental health component scores were calculated and included in the analyses.

Of 729 records from the database of patients completing CR between January 1996 and June 2006, data from 616 records were included in this study. Reasons for excluding the 113 patient records were for the following reasons: nonischemic cardiac diagnoses (n = 40), multiple admissions that followed the index admission (n = 55), and classification of patients other than black or white race/ethnic group (n = 18).

Analyses were completed using Microsoft Excel 2003 (Microsoft, Redmond, WA) and SPSS version 11.5 (SPSS, Chicago, IL). Baseline patient characteristics were summarized with standard descriptive techniques, and differences between racial/ethnic groups were assessed using Student *t* tests (for continuous variables) or χ^2 analyses (for categorical variables). The proportion of patients at secondary prevention goals was compared between groups at entry and at completion of CR.

Table I. Comparison of baseline demographic and clinical characteristics between black and white CR patients who completed the program

Characteristics	Whites n = 459	Blacks n = 157	*P*
Age in years (mean [SD])	62 (10)	61 (10)	ns
Women (n [%])	99 (22)	77 (49)	<.001
Risk factors, n (%)			
Dyslipidemia	409 (89)	136 (87)	ns
Hypertension	325 (71)	145 (92)	<.001
Diabetes	157 (34)	73 (46)	.01
Obesity	191 (42)	69 (44)	ns
Low physical activity	292 (64)	112 (71)	ns
Smoking	65 (14)	30 (19)	ns
AACVPR risk stratification, n (%)			
High	157 (34)	63 (40)	ns
Intermediate	189 (41)	66 (42)	ns
Low	113 (25)	28 (18)	ns
Left ventricular ejection fraction	n = 380	n =135	ns
n (% LVEF <40%)	73 (19)	32 (24)	
Comorbidity index* (mean [SD])	1.5 (1.5)	1.8 (1.7)	.04
Chronic kidney disease	n = 381	n = 135	
n (% GFR <60 mL/m per 1.73 m^2)	109 (29)	42 (31)	ns
Medications (n [%])			
Aspirin	413 (90)	137 (87)	ns
β-Blocker	303 (66)	103 (66)	ns
ACE inhibitor or ARB	272 (59)	188 (69)	.03
Lipid-lowering therapy	346 (75)	115 (73)	ns
Prescribed CR sessions (mean [SD])	28.1 (8.3)	29.8 (8.0)	.03
Attended CR sessions (mean [SD])	28.1 (8.3)	29.6 (7.8)	.04

Continuous variables are described as mean (SD); proportions are described as number (percentage). $P < .05$ was considered statistically significant. *ns*, Not significant; *GFR*, glomerular filtration rate calculated by the abbreviated Modification of Diet in Renal Disease study equation.
*Refer to Zoghbi et al[16] for description and weighting of comorbidities and calculation of the index.

Changes in continuous variables from baseline to CR completion were modeled using a general linear modeling approach, to determine the effect of race/ethnicity on CR outcomes, adjusting for age, gender, baseline value of the variable of interest, and number of CR sessions attended. Each model included terms for race/ethnicity, gender, and the interaction of race/ethnicity and gender. Estimated marginal means, their SEs, and 95% CIs were computed for each race/gender subgroup standardized to the mean age of the population, the mean baseline value for each variable, and the mean number of sessions attended. Additional adjustment for changes in the number of medications from CR entry to completion did not change the results (data not shown).

Results

Baseline characteristics of black and white patients are shown in Table I. Women were substantially more

Table II. Comparison of secondary prevention measures between black and white patients at baseline, at completion, and the change in values from CR entry to completion

	Baseline measures			Completion measures			Change in values		
	Whites	**Blacks**	***P***	**Whites**	**Blacks**	***P***	**Whites**	**Blacks**	***P***
n	459	157		459	157		459	157	
BMI (kg/m^2)	29.6 (5.6)	30.5 (6.9)	ns	29 (5)	30.3 (3.7)*	<.01	−0.6 (1.3)	−0.2 (1.2)	<.001
Waist circumference (in)	40.0 (5.7)	39.4 (5.8)	ns	39.2 (5.5)	39.1 (5.4)*	ns	−0.8 (2.2)	−0.3 (2.4)	.02
Systolic BP	118.6 (18)	126.1 (20)	<.001	117.2 (16)*	122.2 (16)	<.001	−1.5 (17)	−3.9 (21)	ns
Diastolic BP	69.6 (11)	72.9 (12)	<.01	67.7 (10)	69.9 (10)	.02	−1.9 (11)	−2.9 (12)	ns
Total cholesterol (mg/dL)	175 (46)	189 (39)	<.01	156 (33)	169 (43)	<.001	−19 (44)	−19 (48)	ns
LDL-C (mg/dL)	105 (37)	121 (35)	<.001	89 (26)	101 (35)	<.001	−16 (37)	−21 (44)	ns
HDL-C (mg/dL)	38.7 (11)	44.1 (13)	<.001	39.4 (11)*	43.6 (11)*	<.001	0.7 (7.7)	−0.5 (9.7)	ns
Triglycerides (mg/dL)	183 (210)	132 (82)	<.01	146 (103)	124 (76)	.03	−37 (158)	−8 (71)	.04
Non–HDL-C (mg/dL)	135 (44)	145 (37)	.02	116 (31)	125 (41)	<.01	−20 (41)	−19 (46)	ns
HbA_{1c}† (%)	7.4 (1.6)	8.3 (2)	<.01	6.9 (1.2)	8.1 (2.1)*	<.001	−0.6 (1.6)	−0.2 (1.9)	ns
6-min walk distance (ft)	1366 (351)	1076 (372)	<.001	1613 (372)	1284 (377)	<.001	247 (257)	208 (260)	ns
BDI-II	9.0 (7.2)	9.4 (7.6)	ns	5.7 (6.2)	6.5 (6.7)	ns	−3.3 (5.9)	−2.9 (5.5)	ns
SF-36 PCS	37 (10)	33 (10)	<.001	44 (11)	40 (11)	<.001	7 (9)	7 (11)	ns
SF-36 MCS	49 (11)	49 (11)	ns	53 (9)	54 (9)	ns	4 (10)	5 (11)	ns
MEDFICTS diet score	29 (25)	31 (27)	ns	17 (17)	18 (16)	ns	−12 (23)	−13 (25)	ns
Physical activity METhrs	8 (12)	6 (11)	ns	24 (20)	19 (16)	<.01	16 (21)	13 (17)	ns

Continuous variables are described as mean (SD); $P < .05$ was considered a statistically significant difference. *BP*, Blood pressure; *BDI-II*, Beck Depression Inventory II, *SF-36 PCS*, Short-Form Medical Outcomes Study questionnaire, physical component score; *SF-36 MCS*, Short-Form Medical Outcomes Study questionnaire, mental component score.
*Identifies the variables that did not achieve significant differences between CR entry to CR completion when comparing within group changes.
†Hemoglobin A_{1c} measures were only assessed on patients with diabetes.

represented among Blacks (49%) than Whites (22%). The prevalence of hypertension and diabetes was higher in Blacks. Although there was no difference in AACVPR risk stratification between the groups, Blacks had a higher comorbidity index. There was similar use of secondary prevention medications (aspirin, β-blockers, and lipid-lowering therapy) except that a higher proportion of Blacks were on angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACE inhibitors/ARBs). Blacks were prescribed and attended more CR sessions than Whites. Overall, 34% of patients were admitted with a diagnosis of myocardial infarction, 22% after coronary artery bypass grafting, and 44% with stable angina or after percutaneous intervention; there were no gender/ethnic subgroup differences (data not shown).

Table II compares secondary prevention measures at CR entry and completion and the changes in absolute values observed during CR participation between Blacks and Whites. At baseline, Blacks (compared to Whites) had higher blood pressures, more adverse lipid values for total, non–high-density lipoprotein (HDL), and low-density lipoprotein cholesterol (LDL-C) levels. The opposite was observed for triglycerides and HDL cholesterol (HDL-C) levels with Whites having more adverse values. Among patients with diabetes, Blacks had higher hemoglobin A_{1c} levels than Whites, indicating poorer control of blood glucose levels at CR entry. Blacks had lower submaximal functional capacity (6-minute walk distances) and lower perceived health status in the SF-36 physical component score.

Both Blacks and Whites achieved significant improvement from CR entry to completion in most secondary prevention outcomes. High-density lipoprotein cholesterol did not improve in either group. Among Blacks, additional changes that did not reach significance were BMI, waist circumference, triglycerides, and hemoglobin A_{1c} among patients with diabetes. The reduction in systolic blood pressure did not reach significance among Whites, but it did for Blacks. When comparing the measures at CR completion between groups, significant differences between BMI and self-reported physical activity (METhrs) were present that were not observed at baseline. This resulted in a greater number of secondary prevention measures that were more favorable among Whites than Blacks at CR completion than at entry. Although improvement was observed for both Blacks and Whites during CR participation, the amount of improvement in absolute values was greater for Whites in BMI, waist circumference, and triglycerides.

Another approach to evaluate the changes in secondary prevention outcomes between Blacks and Whites was to compare the proportion of patients at each AHA/ACC secondary prevention treatment goal between groups at CR entry and at completion (Table III). At CR entry, a higher proportion of Whites were at goal for blood pressure and lipid management as defined by the current secondary prevention guidelines.[12] At CR completion, Whites retained a higher proportion at goal for blood pressure management and LDL-C, but the difference was no longer significant for the proportion at goal

Table III. Comparison of the proportion of black and white patients at AHA/ACC secondary prevention goal at baseline and completion of CR

Secondary prevention recommendations	Baseline: proportion at goal			Completion: proportion at goal		
	Whites	Blacks	*P*	Whites	Blacks	*P*
Proportion at goal n (%)	n = 459	n = 157		n = 459	n = 157	
Blood pressure management						
No diabetes or CKD present	n = 243	n = 65		n = 243	n = 65	
BP <140/90	207 (85)	51 (78)	ns	211 (87)	54 (83)	ns
Diabetes or CKD present	n = 216	n = 92		n = 216	n = 92	
BP <130/80	138 (64)	43 (47)	<.01	150 (69)	52 (56)	.04
Lipid management						
LDL-C <100 mg/dL	175 (47)	35 (27)	<.001	257 (70)	73 (56)	<.01
Non–HDL-C <130 mg/dL	193 (51)	47 (36)	<.01	262 (69)	81 (62)	ns
Lipid-lowering therapy	346 (75)	115 (73)	ns	360 (78)	121 (77)	ns
Physical activity ≥10 METhrs	120 (27)	32 (21)	ns	374 (84)	105 (70)	<.001
Weight management						
BMI <25 kg/m^2	85 (19)	31 (20)	ns	96 (21)	28 (18)	ns
Waist circumference						
Men	n = 334	n = 72		n = 334	n = 72	
Circumference <40 in	150 (45)	35 (49)	ns	177 (53)	34 (47)	ns
Women	n = 91	n = 71		n = 91	n = 71	
Circumference <35 in	43 (47)	22 (31)	ns	47 (52)	22 (31)	.01
Diabetes management	n = 98	n = 52		n = 98	n = 52	
HbA_{1c}* <7%	29 (30)	11 (21)	ns	43 (44)	13 (25)	.04

P < .05 was considered a statistically significant difference. *CKD*, Chronic kidney disease.
*Hemoglobin A_{1c} measures were only assessed on patients with diabetes.

for non–HDL-C. However, by CR completion, a higher proportion of Whites compared to Blacks had achieved goals for self-reported physical activity (METhrs), hemoglobin A_{1c} of <7% among patients with diabetes, and waist measurement of <35 in among women.

Figure 1 shows the results of the adjusted models for changes achieved in important secondary prevention measures within each race/ethnic and gender subgroup. After adjusting for age, baseline value, number of sessions, and gender, important racial/ethnic differences in the degree of improvement during CR participation were observed. Whites had greater improvements in BMI, waist circumference, LDL-C, 6-minute walk distance, self-reported physical activity (METhrs), and hemoglobin A_{1c} compared to Blacks. Gender differences were observed with greater improvements in LDL-C, non–HDL-C, and self-reported physical activity (METhrs) among men compared to women. By reviewing the individual graphs for each of the measures, it is evident that Black women lag behind Whites and Black men in improvement in most measures. The interaction term for race and gender achieved statistical significance for changes in LDL-C and non–HDL-C and remained significant after adjusting for change in the number of medications from pre- to post-CR.

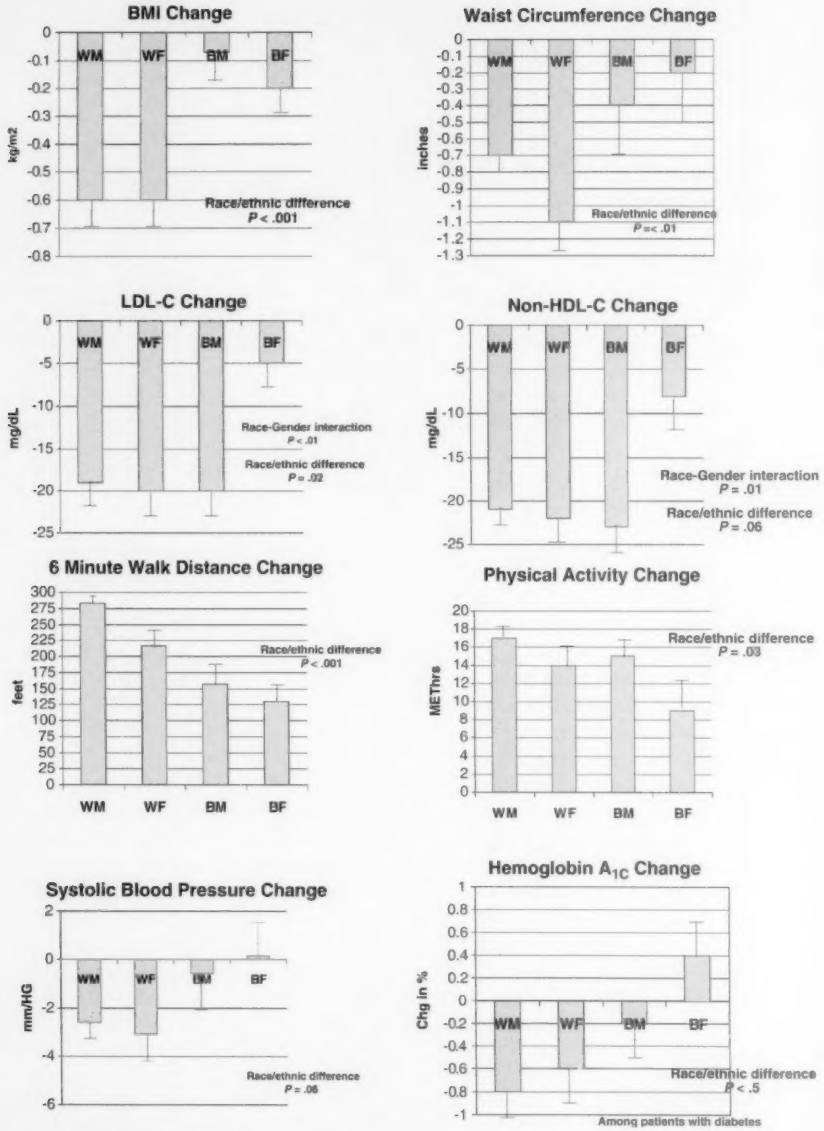
Discussion

To our knowledge, this is the first study that examined baseline characteristics and secondary prevention outcomes relative to the AHA/ACC secondary prevention goals[1,2] in a CR population that included a substantial proportion of Blacks and women. Our sample included 25% Blacks, and among Blacks, 49% were women. We have shown that Blacks entered CR with poorer risk factor profiles than Whites, but both groups achieved significant improvement in most secondary prevention measures by program completion. Furthermore, there was a substantial increase in the proportion at secondary prevention goals for most indicators among both Blacks and Whites. Although we observed clear benefits within each ethnic group at CR completion, there were differences in the degree of improvement between Blacks and Whites for some measures. This was especially evident among Black women.

Differences in baseline characteristics between black and white patients were similar to those previously reported in both epidemiological[1,2] and clinical data sets[9,10,18,19] with a higher prevalence of hypertension and diabetes among black patients. Unlike other studies, we did not observe a higher prevalence of dyslipidemia among Whites[9,10,18,19] or smoking among Blacks.[9,10,19] However, we did observe higher blood pressure and more adverse lipid measurements among Blacks compared to Whites for total cholesterol, LDL-C, and non–HDL-C, and, conversely, Whites had worse HDL-C and triglyceride levels, which is comparable to what is seen in the general US population.[20]

Despite reports of disparities in cardiovascular morbidity and mortality between Blacks and Whites, there is

Figure 1



Changes observed from CR entry to completion in secondary prevention measures that were significantly different ($P < .05$) between black and white patients after adjusting for age, baseline value, number of sessions attended, and gender. Linear regression modeling for changes in each measure is expressed as mean changes and SEM for each race-gender subgroup. *WM*, White male; *WF*, white female; *BM*, black male; *BF*, black female.

limited information about racial/ethnic differences in the provision of recommended secondary prevention treatments or subsequent outcomes. Among this sample of patients completing CR, we found no racial/ethnic differences in the use of aspirin, β-blockers, or lipid-lowering therapy, but more blacks than whites were on ACE inhibitors/ARBs. This finding differs from a study[9] that examined racial variations in evidence-based

treatments for hospitalized patients with acute coronary syndrome where Blacks were less likely to receive lipid-lowering therapy, but were just as likely to receive aspirin, β-blockers, or ACE inhibitors. Because our population was enrolled in CR, the difference in the use of lipid-lowering therapy may be related to a more aggressive approach to secondary prevention overall. The higher use of ACE inhibitor/ARB among Blacks within our population may be related to the higher prevalence of hypertension and diabetes, a population for whom ACE inhibitors/ARBs are recommended for renal protection.

We expected to find CR benefits in both Blacks and Whites and anticipated that the gap between the groups for secondary prevention measures would narrow at CR completion. However, we were surprised to find that the differences in the degree of improvement actually widened the gap between Blacks and Whites (especially among black women) for some important measures. The reasons for this are unclear, but it does bring up important questions related to interventions that are designed to be individualized to the patient, yet may lack specificity to address the unique needs of the patient. Developing more effective secondary prevention interventions that consider personal, behavioral, cultural, and environmental influences in diverse patient populations should be a priority for future research.

Although there is limited information on secondary prevention treatment disparities, there is a paucity of information about secondary prevention outcomes among patients with CHD stratified by both race/ethnicity and gender, even within CR populations. One CR study[21] did compare baseline characteristics and outcomes between black and white women. Although our study included both men and women, we observed similar results of a higher prevalence of baseline hypertension and diabetes among Blacks. Unlike the women-only study,[21] we did not find any racial/ethnic differences in obesity or BMI. This finding was not surprising because our study was restricted to individuals who completed CR, and obesity has been associated with patients not completing CR.[22] Cannistra[21] also reported that only white women lost weight by CR completion. We found that both black men and women lagged behind whites for improvement in BMI and waist circumference. Weight management is a challenging risk-reduction goal, but it appears even more challenging among Blacks participating in CR. Although we found that changes in self-reported diet score were similar between the 2 groups, Blacks did not report the same improvement in physical activity as Whites, which may in part explain the differences in measures of body mass. Similar to 2 other descriptive studies[21,23] that reported functional outcomes among different racial/ethnic groups, we observed improvement in functional capacity after CR in both Blacks and Whites, but with important differences between race/gender subgroups. A most disturbing finding was that black women seemed to lag behind the other subgroups for improvement in not only functional capacity (6-minute walk distance) but also for improvements in waist circumference, LDL-C, non–HDL-C, self-reported physical activity, blood pressure, and hemoglobin A_{1c}. Findings in a large cohort of women with heart disease[24] found that black women less often received appropriate preventive therapy and adequate risk factor control and had >50% higher CHD event risk compared to their white counterparts. In our study, black women received comprehensive secondary prevention services, and although improvement was achieved, it was less than among men and white women. Because traditional risk factors have similar associations with mortality in black and white adults of the same gender,[25] more research is needed to explore the reasons for this differential response to secondary prevention therapies.

There are important limitations to this study. It is descriptive in design with retrospective data analyses of patients completing CR in a single, academic hospital-based setting located in the southeastern region of the United States. Therefore, results may not be representative of patients completing CR in other settings or other geographical regions. This study included only patients who entered and completed CR and does not address factors related to potential racial/ethnic differences in the other stages of CR use including CR referral, enrollment, and attrition.[26] We recognize that differences in the reason for CR referral (medical or interventional therapy) may also influence outcomes, but we analyzed admitting diagnosis by race and gender and found no major imbalances across the diagnostic categories. It is also acknowledged that there are many other factors (educational, socioeconomic, etc) and complex issues that may have contributed to the differences observed between the racial/ethnic groups that were not available for analysis in this clinical data set. Despite these limitations, we believe this observational study has provided some new and important information on secondary prevention outcomes among diverse patient subgroups.

Conclusion

Cardiac rehabilitation/secondary prevention programs are effective in facilitating risk-reduction benefits for both Black and White patients with CHD with significant increases in the proportion of patients at secondary prevention goals from CR entry to CR completion. However, despite the improvement in outcomes within each racial/ethnic group, there remains a benefit gap between Blacks and Whites in important risk factor measures. In an era where reducing disparities in CHD outcomes is a high-priority national goal, there is a paucity of information examining treatment responses

to CHD risk-reduction therapies among high-risk patient subgroups, especially black women. Future research is needed to develop more effective risk-reduction strategies that will address the specific needs of high-risk patient populations. The long-term goal is to aggressively and effectively manage risk factors for all subgroups of the population to eliminate disparities in CHD health outcomes.

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Elevated vascular endothelial growth factor levels are associated with aortopulmonary collateral vessels in patients before and after the Fontan procedure

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Background Aortopulmonary collaterals (APCs) are frequently observed before and after the Fontan procedure. However, the mechanism of the development of APCs is unknown. We hypothesized that one or several antiangiogenic and/or angiogenic growth factors might play a role in the development of APCs.

Methods Eighty-five patients were enrolled and divided into 3 groups (Fontan group: 30 patients after the Fontan procedure, cyanotic group: 29 patients with cyanotic heart disease, and control group: 26 patients with cyanotic heart disease after biventricular repair). We measured basic fibroblast growth factor, vascular endothelial growth factor (VEGF), hepatocyte growth factor, and endostatin at catheterization. Angiographic evaluation for the presence of APCs using a 4-point scale (grade 1: absent APCs, ≥grade 2: significantly present APCs) was performed, and the relation of the serum levels of these factors to the presence of APCs was assessed.

Results The grade of APCs significantly increased in the Fontan group, but it decreased in the control group. The serum VEGF levels were higher in the Fontan group (280 ± 174 pg/mL) and the cyanotic group (302 ± 245 pg/mL) than in the control group (111 ± 91 pg/mL) ($P = .0004$), and they were higher in patients with APCs (383 ± 204 pg/mL) than in those without APCs (115 ± 65 pg/mL) ($P < .0001$). There was no significant difference in the serum basic fibroblast growth factor, hepatocyte growth factor, and endostatin levels between the 3 groups.

Conclusions Aortopulmonary collaterals increase after the Fontan procedure. Serum VEGF levels are associated with the presence of APCs. Vascular endothelial growth factor may play a role in the development of APCs in patients with cyanotic heart disease and after the Fontan procedure. (Am Heart J 2007;153:987-94.)

Aortopulmonary collateral vessels (APCs) are frequently observed in patients before and after the Fontan procedure.[1-3] Several studies have suggested that the APCs are one of the risk factors for the outcome of the Fontan procedure and can even be associated with a higher mortality.[3,4] Therefore, transcatheter coil embolization of collaterals has been attempted before and/or after the Fontan procedure.[1,2] However, the mechanism of the formation of these collaterals remains unknown. Several angiogenic growth factors and/or antiangiogenic factors play a major role in the development of abnormal blood vessels.[5-11] A balance of angiogenic growth factors and antiangiogenic factors mediates the development of these collaterals. Angiogenic growth factors include vascular endothelial growth factor (VEGF),[5-7] basic fibroblast growth factor (b-FGF),[7] and hepatocyte growth factor (HGF).[8,9] Endostatin is an antiangiogenic factor.[10,11] Inhibition of these growth factors or administration of antiangiogenic factors may be an alternative treatment to coil embolization.[12] In addition, it is not clear whether APCs observed in patients with chronic cyanosis disappear after improvement of the cyanosis. In our experience, APCs were observed after the Fontan procedure, although cyanosis was completely eliminated. Therefore, the present study was undertaken to examine the following hypotheses: (1) APCs observed in patients with chronic cyanosis may increase further after the Fontan procedure and (2) one or several angiogenic growth factors and antiangiogenic factors may play a

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Table I. Demographic data of the 3 study groups

	Control group (n = 26)	Fontan group (n = 30)	Cyanotic group (n = 29)	P
Age at catheterization (y)	5.8 ± 3.6	6.9 ± 5.6	4.2 ± 4.6	.09
Interval from last operation to catheterization (y)	2.6 ± 3.0	2.4 ± 3.7	3.0 ± 4.0	.80
Hypoxic periods (y)	3.2 ± 3.0	4.6 ± 2.8	4.2 ± 4.6	.32
Previous surgery				
B-T shunt (% of pts)	50	67	52	.37
PAB (% of pts)	12	20	21	.62
AO saturation, preoperative. (%)	83 ± 7	81 ± 5	81 ± 5	.31
AO saturation, postoperative (%)	97 ± 1	95 ± 1	–	<.0001

pts, Patients; *B-T shunt*, Blalock-Taussig shunt; *PAB*, pulmonary artery banding; *AO*, aortic oxygen.

role in the development of APCs in patients after the Fontan procedure.

Methods

Study patients

This study included 85 patients in whom blood samples were collected during cardiac catheterization and angiogenic growth factors and antiangiogenic factors were analyzed. The patients were divided into 3 groups: 30 patients who had undergone the Fontan procedure (Fontan group), 29 patients with cyanotic heart disease (cyanotic group), and 26 patients with cyanotic heart disease who had undergone biventricular repair (control group). Patients were prospectively excluded from the Fontan and control groups if they met the following criteria: (1) existence of intracardiac right-to-left shunts because of a fenestrated Fontan procedure and/or systemic venous channels,[13] (2) time interval ≤6 months between the intracardiac repair (including Fontan operation) and postoperative catheterization because the major surgery itself is associated with a transient increase in the serum VEGF levels,[14] and (3) preoperative cineangiography not available for review. In the Fontan group, the type of Fontan procedure was atriopulmonary anastomosis in 21 and total cavopulmonary anastomosis in 9 patients. In the control group, the type of biventricular repair was intracardiac repair in 12, Rastelli-type operation in 9, and arterial switch operation in 5 patients. In the cyanotic group, 18 patients were Fontan candidates, and the others were candidates for biventricular repair. Because a bidirectional Glenn operation was not routinely performed before the Fontan procedure during the study periods, almost all Fontan candidates did not have this palliative operation in our hospital. Therefore, patients after the bidirectional Glenn procedure were not included in this study. Our institutional review board approved the clinical study, and patients or their parents gave informed consent before the catheterization.

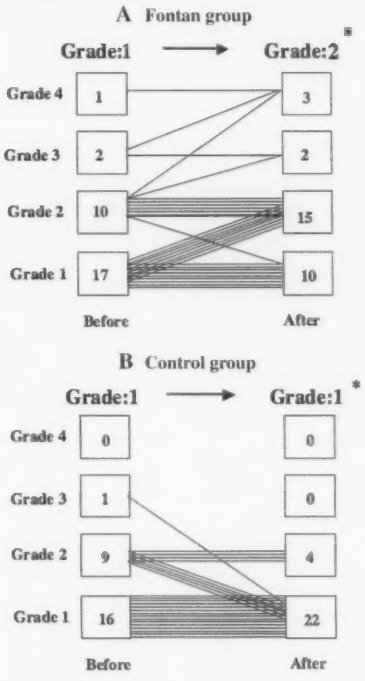
Angiograms

Pulmonary angiography and aortography were performed in all patients. Selective power injection into the brachiocephalic, subclavian, bronchial, and/or intercostal arteries was performed in 16 patients in the Fontan group, in 10 patients in the cyanotic group, and in 12 patients in the control group. Attempts were made to identify significant APCs by these angiograms. Step-up oxygen saturation in the pulmonary artery was also a clue for the identification of APCs. If visualized, APCs were graded on a 4-point scale using the modified method described by Spicer et al.[5] Grade 1 collaterals were <3, <2 mm, and did not opacify the pulmonary arteries or veins. Grade 2 collaterals were multiple and small but included a few larger vessels and did not opacify the pulmonary arteries or veins. Grade 3 collaterals were similar to those of grade 2 or slightly increased in size and number but opacified the pulmonary arteries and/or veins. Grade 4 collaterals were multiple large vessels with angiographic opacification. Two observers (Y.M. and T.F.) independently graded APCs. When there was disagreement between the 2 observers, the higher grade of APCs was used in the final analysis. Collaterals >grade 2 were considered as significant APCs on the basis of angiogenesis in this study, although treatment for the APCs, such as coil embolization, was indicated in those >grade 3. In the Fontan and control groups, cineangiograms before surgery were also reviewed. The collaterals were graded from preoperative cineangiograms using the same method, and the grade of collaterals was compared between pre- and postoperative states. Ten selective power angiograms before and after surgery were available for comparison in the Fontan group and 6 in the control group. The others were compared using aortograms.

Measurements of serum antiangiogenic and angiogenic growth factors

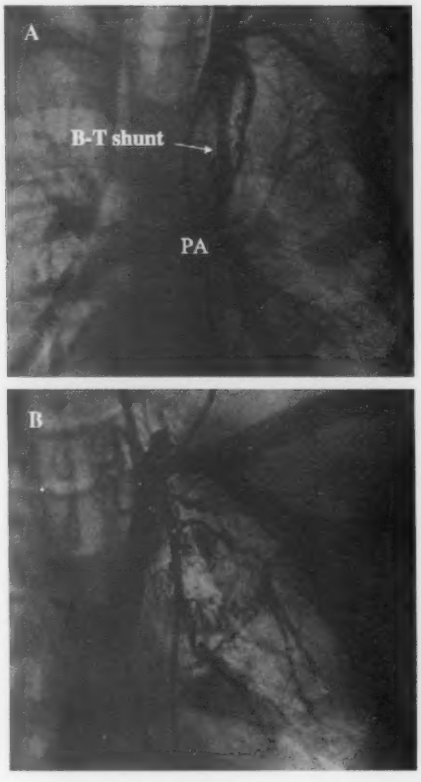
To determine the source of antiangiogenic and/or angiogenic factors, blood samples were obtained from the superior vena cava, inferior vena cava (at the position just below the right atrium), and a systemic artery during catheterization before administration of heparin because heparin has been shown to affect serum angiogenic factor levels.[9] After centrifugation, the separated serum was stored at −70°C, until assays were performed. Serum VEGF, b-FGF, HGF, and endostatin levels were measured by enzyme immunosorbent assay using commercially available kits (VEGF, b-FGF, and endostatin: Quantikine, R&D systems, Minneapolis, MN, and HGF: Otsuka Assay Laboratories, Tokyo, Japan). This enzyme immunosorbent assay can detect both VEGF 165 and VEGF 121. The intra- and interassay variations were 6.9% and 6.6% for VEGF, 6.9% and 8.2% for b-FGF, 4.2% and 7.7% for HGF, and 6.3% and 9.0% for endostatin, respectively. The minimum level of detection was 9.0 pg/mL for VEGF, 3.0 pg/mL for b-FGF, 0.01 ng/mL for HGF, and 0.01 ng/mL for endostatin.

Figure 1



Changes in the grade of APCs in the Fontan and control groups. Numbers in the boxes indicate numbers of patients. Note that the grade of APCs increased in the Fontan group, although it decreased in the control group. *$P < .05$ compared with the grade of APCs before surgery. The number on top indicates the median of grades before and after surgery.

Figure 2



Example of selective left subclavian angiograms at the same phase in a patient with APCs before (grade 2) (**A**) and after (1 year 3 months later, grade 3) the Fontan procedure (**B**). Note that the number and size of the APCs arising from the left internal mammary artery and the lateral thoracic and thoracodorsal arteries increased after the Fontan procedure. *B-T shunt*, Blalock-Taussig shunt; *PA*, pulmonary artery.

Analysis of the number of platelets

Because platelets have been shown to be a rich source of VEGF,[15] the number of platelets was compared between the groups, and before and after surgery in the Fontan and control groups.

Statistical analysis

Continuous data were expressed as mean ± SD and qualitative data as percentages. Average concentrations for 3 sampling sites were used for comparison between the groups. Differences between 2 groups were evaluated with Student *t* test or the Wilcoxon signed rank test when appropriate. Analysis of variance followed by Scheffe procedure was used to compare continuous variables for >2 mean values. Comparison of categorical variables was made using the Fisher exact test. Correlation between the serum VEGF levels and hemodynamic variables including aortic oxygen saturation was tested with Pearson correlation coefficient. All statistical analyses were performed with Stat View, version 5.0 (SAS Institute, Cary, NC). $P < .05$ was interpreted to denote statistical significance.

Results

The demographic data of the study patients are summarized in Table I. The history of previous surgery, such as Blalock-Taussig shunt and pulmonary artery banding, including the number of times thoracotomy was performed, was similar between the groups. Because the coronary sinus was cut back into the left atrium in the Fontan patients, the postoperative aortic oxygen saturation obtained at catheterization in the Fontan group (95% ± 1%) was slightly but

Table II. Serum levels of angiogenic growth factors and antiangiogenic factors from the 3 sampling sites

	Control group				Fontan group				Cyanotic group			
	SVC	IVC	Ao	P	SVC	IVC	Ao	P	SVC	IVC	Ao	P
b-FGF (pg/mL)	12.7 ± 11.3	14.5 ± 13.0	13.7 ± 15.5	.9	15.9 ± 14.4	19.1 ± 19.9	17.2 ± 16.6	.78	21.8 ± 24.5	18.0 ± 11.8	20.5 ± 12.2	.74
HGF (ng/mL)	0.89 ± 1.03	0.80 ± 0.89	0.66 ± 0.75	.69	0.65 ± 0.32	0.65 ± 0.31	0.59 ± 0.33	.75	0.78 ± 0.89	0.89 ± 0.43	0.67 ± 0.34	.35
VEGF (pg/mL)	101 ± 102	91 ± 100	114 ± 88	.75	289 ± 191	274 ± 200	191 ± 193	.94	266 ± 247	309 ± 271	375 ± 320	.48
Endostatin (ng/mL)	7.1 ± 3.3	7.1 ± 2.9	7.2 ± 3.1	.97	10.2 ± 5.4	9.2 ± 5.2	10.4 ± 6.1	.74	9.2 ± 5.7	8.8 ± 4.9	8.0 ± 4.3	.72

SVC, Superior vena cava; *IVC*, inferior vena cava; *Ao*, aorta.

significantly lower than that in the control group (97% ± 1%) (Table I).

Aortopulmonary collaterals

The 2 observers disagreed on the grade of APCs in 10 (7.1%) of 141 cases. In 2 cases, disagreement occurred between grades 3 and 4, and in 8 cases, between grades 2 and 3. No discrepancy occurred between grades 1 and 2. Significant APCs ≥grade 2 were observed in 20 (67%) of the 30 Fontan patients (grade 2 in 9, grade 3 in 8, and grade 4 in 3 patients). In the cyanotic group, significant APCs were found in 13 (45%) of the 29 patients (grade 2 in 6, grade 3 in 5, and grade 4 in 2 patients). In the control group, significant collaterals ≥grade 2 were detected in 4 (15%) of the 26 patients (all grade 2). Coil embolization was performed in 6 patients with collaterals ≥grade 3 (2 patients in the Fontan group and 4 in the Fontan candidates of the cyanotic group).

When the grade of APCs was compared between pre- and postoperative states using the same angiographic technique, it was found to have significantly increased in the Fontan group ($P = .02$). In contrast, the grade of APCs had decreased in the control group ($P = .03$). Thus, APCs developed even after the cyanosis had improved in patients after the Fontan procedure. However, the grade of APCs after the Fontan procedures was underestimated because the selective power angiographic technique was used less frequently in the serial study (grade 2 in 15, grade 3 in 2, and grade 4 in 3 patients) (Figures 1 and 2).

Hemodynamic data

In each group, mean right atrial pressure, pulmonary artery pressure, left atrial pressure, and systemic aortic pressure were similar between the patients with and without APCs (all variables for each group $P > .1$). Pressure gradients between the pulmonary artery and pulmonary vein pressure and the cardiac index were also similar between the patients with and without APCs in each group (both variables for each group $P > .1$).

Comparison of serum angiogenic growth factors and antigrowth factor levels among the 3 groups

Serum levels of b-FGF, HGF, VEGF, and endostatin from the 3 sample sites are shown in Table II. There was no significant difference between the sample sites in each group.

When the average levels for the 3 sample sites were taken, the serum levels of b-FGF and HGF were similar between the 3 groups. Serum endostatin levels were also similar between the 3 groups. However, the serum VEGF levels were significantly higher in the Fontan group (280 ± 174 pg/mL) and the cyanotic group (302 ± 245 pg/mL) than in the control group (111 ± 91 pg/mL) ($P = .0004$). There was no significant difference in the serum VEGF levels between the Fontan and cyanotic groups (Figure 3).

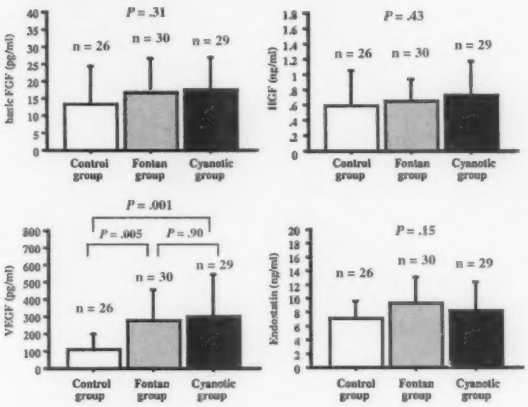
Relation between development of APCs and serum VEGF levels

The serum VEGF levels were significantly higher in patients with APCs ≥grade 2 (383 ± 204 pg/mL) than in those without APCs (115 ± 86 pg/mL) ($P < .0001$). The VEGF levels were similar between the 3 subgroups with significant APCs ≥grade 2 (Figure 4). Also, these levels were higher in patients with APCs than in those without APCs in each group (Figure 5). There were no significant differences in the serum levels of other factors between the patients with and without APCs (b-FGF 17.9 ± 10.7 pg/mL with APCs vs 14.0 ± 8.5 pg/mL without APCs, $P = .07$; HGF 0.64 ± 0.29 ng/mL with APCs vs 0.67 ± 0.47 ng/mL without APCs, $P = .68$; endostatin 9.0 ± 4.1 ng/mL with APCs vs 7.5 ± 3.3 ng/mL without APCs, $P = .11$).

Relation between serum VEGF levels and other factors

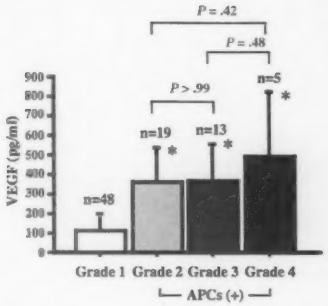
There was no correlation between serum VEGF levels and hemodynamic variables such as systemic venous pressure, mean pulmonary artery pressure, and pressure gradient between mean pulmonary artery and venous pressure, but a weak correlation of −0.24 ($P = .04$) was found between cardiac index and serum VEGF levels.

Figure 3



Averaged b-FGF, HGF, VEGF, and endostatin levels for the 3 sites sampled (superior vena cava, inferior vena cava, and systemic artery) in the 3 groups.

Figure 4



Serum VEGF levels in patients without (grade 1) and with (grades 2-4) significant APCs. * $P < .0001$ compared with the group of grade 1.

Also, there was no correlation between serum VEGF levels and aortic oxygen saturation ($P = .08$). However, a weak but significant correlation of −0.34 was found between the serum VEGF levels and aortic oxygen saturation when the Fontan group was excluded ($P = .01$). The number of platelets did not correlate with circulating VEGF levels, and it was similar between the 3 groups (Fontan group $29.9 \pm 9.3 \times 10^4/\mu L$, cyanotic group $29.0 \pm 6.9 \times 10^4/\mu L$, control group $30.5 \pm 6.9 \times 10^4/\mu L$, $P = .81$). Also, the number of platelets at the time of hospitalization for the cardiac catheterization before and after the Fontan procedure was $29.3 \pm 9.4 \times 10^4/\mu L$ and $29.9 \pm 9.3 \times 10^4/\mu L$, respectively ($P = .99$). In the control group, it was $27.4 \pm 7.1 \times 10^4/\mu L$ before and $30.5 \pm 6.9 \times 10^4/\mu L$ after the repair ($P = .17$). Thus, the number of platelets did not change between the pre- and postoperative states in both groups.

Discussion

The present study is the first to demonstrate that elevated VEGF levels are associated with the presence of APCs in patients with cyanotic heart disease and after the Fontan procedure and that APCs observed in patients with chronic cyanosis do not disappear or increase further after the Fontan procedure.

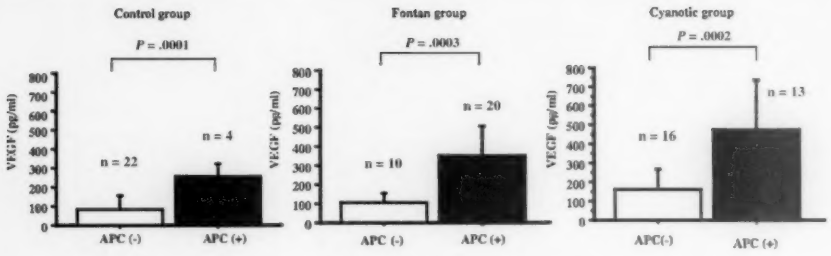
Aortopulmonary collateral vessels after Fontan procedures

It is well documented that APCs develop in patients with cyanotic heart disease[16] and in Fontan candidates, including those after the Glenn operation.[1,2] These collaterals have also been observed at catheterization in patients after the Fontan procedure.[1-4] Triedman et al[1] reported a 30% incidence of APCs in children who had a mean aortic oxygen saturation of 86% after the Fontan procedure, and Bridges et al[2] found that 20% of children after the fenestrated Fontan operation had APCs. Their definition of significant APCs was ≥grade 3.[1,2] In our study, significant APCs (≥grade 2) were observed in 67% and APCs ≥grade 3 in 37% of the Fontan patients. The incidence depends on the definition of significant APCs and the angiographic technique used.[1,17]

Of note, the Fontan patients we studied were not cyanotic, as indicated by their mean aortic oxygen saturation of 95%. Previous studies have suggested that the development of APCs is related to chronic cyanosis because the systemic aortic saturation remained decreased in all patients with APCs even after the Fontan procedure.[1-4] We demonstrated that the APCs developed or did not disappear in almost all of the patients at about 2 years after the Fontan procedure, although cyanosis disappeared at rest. In contrast, the APCs observed in patients with cyanotic heart disease decreased after biventricular repair (control group).

In Fontan patients, significant APCs result in a left-to-right shunt and increase volume load on the systemic ventricle. Blood flow from the APCs competes with systemic venous flow through the pulmonary vascular bed. Although the adverse effects of these collaterals on the outcome of the Fontan procedure are still controversial,[17] several studies have suggested that patients with these acquired APCs have prolonged pleural effusion after surgery and can even have a higher mortality of operation.[3,4] Therefore, transcatheter coil embolization of collaterals has been attempted to abolish

Figure 5



Serum VEGF levels in patients with and without APCs in the 3 groups.

or decrease the shunt before and/or after Fontan procedures.[1-4,17]

Circulating angiogenic growth factor levels

The etiology of the development of these collaterals is unknown, but there are several possibilities. Firstly, the abnormal physiologic characteristics of pulmonary blood flow, including decreased or absent pulsatility and decreased volume and velocity, may induce the development of APCs. One can also speculate that it is the result of chronic hypoxia and an adaptive mechanism to deliver more blood in the case of decreased pulmonary blood flow.

Recent studies have shown that VEGF, b-FGF, and HGF, referred to as angiogenic growth factors, stimulate the development of collateral arteries in animal models of ischemic heart disease.[6-8] Several investigators have found that circulating levels of angiogenic growth factors are elevated[18,19] and that these factors play a role in the improvement of the ischemic regions by promoting angiogenesis in patients with acute myocardial infraction.[20,21] Thus, circulating levels of angiogenic growth factors reflect ongoing angiogenesis. These angiogenic growth factors have been shown to be up-regulated endogenously in response to hypoxia.[5,21] In this respect, several studies have suggested that VEGF, but not b-FGF or HGF, plays a role in the development of APCs in patients with cyanotic congenital heart disease.[22-24] A serial study demonstrated that elevated VEGF levels in patients with cyanotic heart disease decreased to similar levels as in patients with postoperative acyanotic heart disease after biventricular repair.[24] A recent in vitro study showed that VEGF in patients with cyanotic congenital heart disease functionally contributed to angiogenic activity.[25] However, these studies did not show any relation between elevated VEGF levels and the presence of APCs. The present study demonstrated that serum VEGF levels were not only elevated in patients with cyanotic congenital heart disease but also had a significant relationship with the development of APCs.

Another important finding in our study was that serum VEGF levels were still elevated in the Fontan patients, and they were associated with the presence of APCs, although the hypoxic condition was completely converted to a nonhypoxic state. Thus, the serum VEGF levels, which were up-regulated in response to hypoxia, did not decrease after the Fontan procedure for an average of 2 years. These data indicate that the formation of APCs observed in patients with cyanotic heart disease and the Fontan patients could be mediated by VEGF.

However, it is not clear why the circulating VEGF levels remained elevated in the Fontan patients even after the systemic hypoxia disappeared. One possibility is that shear stress (ie, elevated systemic venous pressure observed in the Fontan patients) on the blood vessels or cells such as the platelets may promote the production of VEGF. However, no relation was found between the serum VEGF levels and systemic venous pressure and the number of platelets in our study. Several studies have shown that systemic aortic oxygen saturation decreases during exercise in Fontan patients who are in an acyanotic state at rest.[26] Although the decrease in systemic aortic oxygen saturation is small, some degree of hypoxia may occur at the tissue level. This may be related to our findings that systemic VEGF levels were elevated in the Fontan patients.

Circulating antiangiogenic factors

In addition to angiogenic growth factors, it is possible that antiangiogenic factors may also play a role in the development of abnormal blood vessel formation. Endostatin suppresses angiogenesis by inhibiting the proliferation and migration of endothelial cells.[10] A recent study showed that pericardial fluid endostastin levels were reduced in patients with ischemic heart disease who had significant coronary artery collaterals, suggesting that endostatin modulates coronary collateral

formation locally.[11] However, serum endostatin levels measured in this study were not reduced in patients with APCs. Endostastin is a C-terminal fragment of collagen XVIII, which is present in all basement membranes of many tissues and localized mainly in a perivascular position around blood vessels.[10] Even if it is reduced locally in ischemic tissue, assessment of circulating endostatin levels does not necessarily show the local levels. Another possibility is that a different mechanism is involved in the development of APCs in patients with cyanotic congenital heart disease or after the Fontan procedure from that of coronary collateral formation in patients with ischemic heart disease.

Interestingly, serum endostatin levels from the 3 sampling sites did not differ. It is well known that pulmonary arteriovenous malformation, which is a different type of abnormal blood vessel formation from APCs, develops after some types of cavopulmonary anastomosis. Several studies have demonstrated that the development of pulmonary atriovenous malformation was related to the diversion of normal hepatic flow, and it was due to the absence of the so-called hepatic factor.[27] The hepatic factor could be an antiangiogenic factor because the pulmonary arteriovenous malformation resolved after the return of hepatic venous blood into the pulmonary circulation.[28] In this sense, our data suggest that the hepatic factor is not endostatin, because serum endostatin levels in the inferior vena cava containing hepatic venous blood did not differ from those in the superior vena cava or systemic arteries.

Study limitations

Firstly, the angiographic visualization of collaterals depends on the investigator's techniques. We did not perform the selective power injection for assessment of the grade of APCs in all patients. However, assessment of APCs of grade 1 or >2 (ie, nonsignificant APCs or significant APCs) was similar between the selective angiograms and aortograms in the present study. Secondly, it is necessary to evaluate changes in serum VEGF levels serially before and after the Fontan procedure and biventricular repair to confirm that they do not decrease in patients after the Fontan procedure. Finally, the source of circulating VEGF was not determined. Organs such as the lung, liver, and heart are a rich source of VEGF, and various types of cells, including vascular smooth muscle cells and blood cells, also contain VEGF,[15] as described. The strategy of assessment of circulating levels from different sites might be predicted to be unsuccessful because of rapid equilibration and dilution of factors produced by a given organ. A recent study showed that patients after cavopulmonary shunt had increased staining for VEGF and its receptor in the lung.[29] It may be necessary to search at the tissue level to identify the source.

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Long-term patency of internal thoracic artery grafts for coronary artery stenosis due to Kawasaki disease: Comparison of early with recent results in small children

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Background The results of coronary artery bypass grafting using the internal thoracic artery (ITA) had been reported less satisfactory in patients <12 years old with coronary artery lesions caused by Kawasaki disease.

Methods Since 1983, 67 patients have undergone this operation in our hospital; their age at operation ranged from 1 to 59 years (median 11 years), and the total number of ITA grafts was 95. The interval from operation to latest graft patency as confirmed by angiogram or echocardiogram ranged from 4 months to 23 years (median 8 years). For analysis of graft patency rates, patients were divided into 4 groups based on year of coronary artery bypass grafting and age when grafted. The groups based on year were from 1983 to 1993 (early) and from 1994 to 2006 (later), whereas the age groups were age at operation <12 years and age at operation ≥12 years. From 1999, percutaneous transluminal balloon angioplasty was performed for postoperative anastomotic stenosis.

Results Percutaneous transluminal balloon angioplasty for anastomotic stenosis in ITA graft was performed in 6 patients. When the age at operation was <12 years, the 10-year patency rate in the later period was 94.4% (n = 18), significantly > the 70.0% (n = 30) seen in the earlier period ($P < .05$).

Conclusion Recent results of ITA grafts in patients <12 years old have improved through the application of appropriate indications and percutaneous transluminal balloon angioplasty for anastomotic stenosis. Once good flow in the ITA 1 year after surgery is confirmed, graft patency will persist >20 years. (Am Heart J 2007;153:995-1000.)

Coronary artery bypass grafting (CABG) using a saphenous vein (SVG for stenotic lesions due to Kawasaki disease [KD]) has been done since 1975, and internal thoracic artery (ITA) grafts were initiated into Japan in 1983.[1,2] The Japanese experience of CABG for KD coronary sequelae was reported in 2002.[3] The results of grafting using the ITA were good in patients ≥12 years old but were less satisfactory in patients <12 years old.[4] We reviewed our results of CABG using the ITA, focusing on graft patency in patients <12 years old.

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Methods

Patient population

We identified 67 patients who had undergone CABG with the ITA in our hospital since 1983, 48 (72%) males and 19 (28%) females. Six patients have had a reoperation, 3 of whom had initially undergone CABG with an SVG. Since 1983, a total of 71 operations have been done. The age at operation ranged from 1 to 59 years (median 11 years), and the interval from the onset of KD to operation was 2 months to 45 years (median 7 years). One patient also underwent mitral valvuloplasty. Seven adult patients had undergone off-pump CABG.

Coronary artery bypass grafting

The number of grafted vessels was single vessel, 42 (59%); 2 vessels, 21 (30%); 3 vessels, 6 (8%); 4 and 5 vessels, 1 (1.5%) each. The mean number of grafts was 1.6 per patient. Grafts used were the ITA, 85 (73%); SVG, 17 (15%); gastroepiploic artery, 3 (3%); combined ITA with radial artery (RA), 10 (9%). The combined ITA grafts with RA were performed in adult patients. The total number of ITA grafts including ITA grafts combined with RA was 95, and the grafted coronary arteries were the left anterior descending artery (LAD), 68 (72%); the right coronary artery (RCA), 18 (19%); the left circumflex

Table I. Details of the respective groups

	1983-1993		1994-2006	
	<12 y	≥12 y	<12 y	≥12 y
No. of grafts	30	14	18	33 (10)*
No. of patients	25	12	14	20
Mean age ± SD at surgery (y)	6.5l ± 3.1	16 ± 3.2†	6.1 ± 2.4	25 ± 13†
Mean age ± SD at follow-up (y)	15l ± 6.7	14 ± 7.4	4.7 ± 4.1	5.2 ± 4.9
PTBA	0	0	5	1
Medication				
Antiplatelets	22 (83%)	10 (83%)	14 (100%)	20 (95%)
Warfarin	6 (24%)	0	4 (27%)	1 (5%)
None	3	2	0	1

*Value in parentheses corresponds to the number of composited ITA grafts with RA.
†$P < .05$, significant difference between 2 groups regarding age at operation.

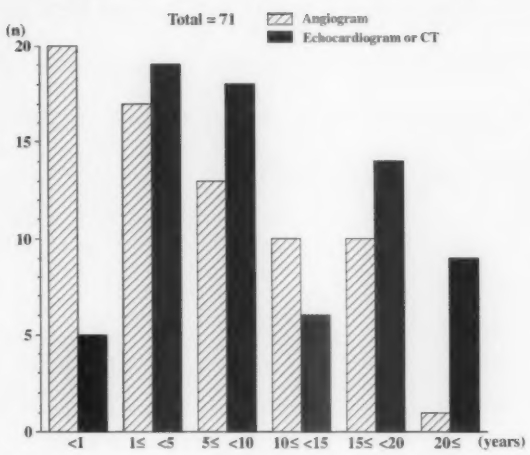
(posterolateral, posterior descending), 5 (5%); the obtuse marginal branch, 3 (3%); and the diagonal branch, 1 (1%).

Acute KD management included aspirin, intravenous immunoglobulin, and steroids in 29 (43%) patients, 19 (28%) patients, and 7 (10%) patients, respectively. Thirty-one (46%) patients had no active treatment. Pre-CABG myocardial infarction occurred in 15 (22%) patients, and 4 (6%) patients had a history of ≥2 myocardial infarction episodes. Other preoperative symptoms were present in 8 (12%) patients, including syncope on exertion in 3 patients and chest pain in 5. There were 4 (6%) patients who were symptomatic at the time of examination. Three complained of chest pain and 1 of syncope. The presence of myocardial ischemia was evaluated by ≥1 of the following: Master double step test, treadmill test, dipyridamole-loaded or exercise radioisotope myocardial imaging, dipyridamole-loaded 12-lead electrocardiogram, dipyridamole-loaded body surface mapping, and dipyridamole-loaded electron beam tomography. Sixty-five patients had ischemic findings in at least 1 examination. Strong ischemia has been needed for indication of CABG since 1994.

We retrospectively analyzed the graft patency in patients who underwent ITA CABG from 1983. Grafts were classified as patent, string sign, or occluded based on postoperative angiography. For this study, a string sign was regarded as occluded. Angiograms were performed according to our standard follow-up protocol. Until 1998, the first angiogram was done within 1 month after surgery; a second angiogram 1 year after surgery; and subsequent angiograms 5 years, 10 years, and 15 years postoperation. Since 1999, the first angiogram was performed the second week after surgery and a second angiogram 3 months after surgery in small children and in cases with anastomotic stenosis in the first angiogram. When anastomotic stenosis >75% is detected, percutaneous transluminal balloon angioplasty (PTBA) is planned. Since 2002, the follow-up angiograms 1 year, 10 years, and 20 years after surgery were performed by 16-detector-row computed tomography in patients >12 years old.[5] Each year, flow in the ITA graft is confirmed by transthoracic echocardiography.

For analysis of graft patency rates, patients were divided into 4 groups based on year of CABG and age when grafted. The groups based on year of CABG were from 1983 to 1993 (early) and from 1994 to 2006 (later), whereas the age groups were age at operation <12 years and age at operation ≥12 years. The number of patients in each group is shown in Table I as well as the number of grafts and the mean age ± 1 SD at operation. The differences in graft patency rates in the groups were investigated with 2 factors in view: first, the degree of stenosis of the grafted vessels, and second, the use of PTBA for anastomotic stenosis.

Figure 1



Number of patients by interval from operation to latest angiogram and from operation to the latest confirmation of graft patency. *CT*, Multi-slice spiral computed tomography.

Postoperative angiogram and confirmation of graft patency

All patients underwent postoperative angiography. The interval from operation to the latest angiogram ranged from 10 days to 22 years (median 5 years). The age at the latest confirmation of graft patency by angiography or echocardiography ranged from 4 months to 23 years (median 8 years). The number of patients by interval from operation to their latest angiogram and by interval from operation to the latest confirmation of graft patency is shown in Figure 1.

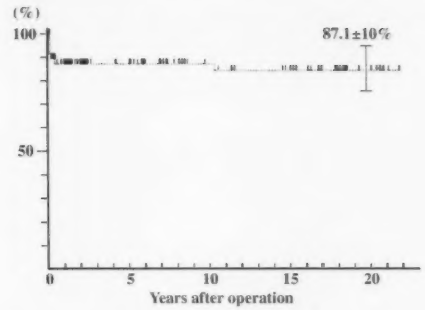
Data analysis

Graft patency rates were analyzed by the Kaplan-Meier method, and differences were assessed by the Cox-Mantel test. Differences were considered statistically significant at $P < .05$. The unpaired t test and the Fisher test were used to compare the differences between groups.

Results

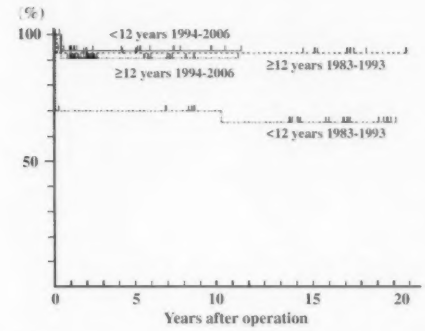
Three (4%) patients died. One died 4 years after cardiac transplantation. He had intractable cardiac failure before CABG. His graft remained patent until his heart transplantation. The other 2 deaths were sudden.

Figure 2



Patency rates of ITA grafts. The values obtained by analysis are shown as the mean ± SE.

Figure 3



Patency rates of ITA grafts in the early term and the later term.

One patient had undergone CABG of the ITA to the LAD at the age of 18 months in 1987. He died 2 months later. Autopsy showed a patent graft and a thrombotic occlusion in a distal coronary aneurysm of the anastomosis. The other patient with low left ventricular ejection fraction and nonsustained ventricular tachycardia died at the age of 26 years. Although she had undergone ITA grafts to the LAD in 1992 and 1998, both grafts showed a string sign.[6] The status of the 64 survivors was New York Heart Association class I. Three female patients had delivered children. The left ventricular ejection fraction by the latest left ventriculography was ≥50% in 59, <50% to ≥40% in 4, and <40% in 4. Of the 3 patients who died, 2 had a left ventricular ejection fraction <40%.

There was no significant difference between the early and the later groups for patients <12 years old regarding the age at operation and anticoagulant therapy after CABG (Table I). Although there was a significant difference between the early and the later groups for patients ≥12 years old regarding age at operation ($P < .05$), there was no significant difference regarding anticoagulant therapy between the groups.

Table II. Coronary artery lesions of grafted vessels and number of graft occlusions in respective groups

Target vessels	Degree of stenosis	1983-1993		1994-2006	
		<12 y	≥12 y	<12 y	≥12 y
LAD	100	8 (1)	5	4 [1]	9
	SS	3 (3)		1	
	90	1	1	4 [1]	3
	75	5 (1)	2 (1)	5 [2]	4 [1] (1)
	50	8 (5)	3	1 (1)	1 (1)
RCA	100	3	1		5
	SS	1		1	1
	90			1 [1]	2
	75	1			1
	50				1 (1)
PL	100		1	1	2
	90				1
	50				1
OM	100		1		
	75	1			1
DX	90				1
Total		30 (10)	14 (1)	18 [5] (1)	33 [1] (3)

Values in brackets correspond to the number of successful PTBAs. Values in parentheses correspond to the number of graft occlusions. *PL*, Posterolateral branch; *OM*, obtuse marginalis; *DX*, diagonal branch; *SS*, segmental stenosis.

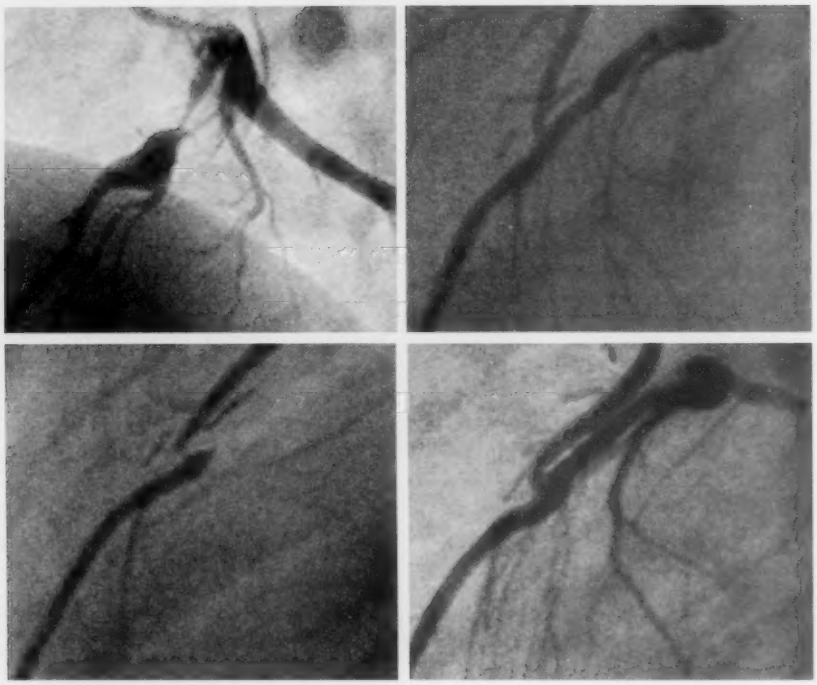
Graft patency

The combined ITA-RA grafts were successful in all 10 patients. Overall patency rates for ITA grafts at 1, 10, and 20 years were 89.1%, 87.1%, and 87.1%, respectively (n = 95) (Figure 2). When the age at operation was ≥12 years in the early period, patency rates at 1, 10, and 20 years were 92.8%, 92.8%, and 92.8%, respectively (n = 14). For age at operation <12 years, the rates at 1, 10, and 20 years were 70.0%, 70.0%, and 66.7%, respectively (n = 30) (Figure 3). In the later period, when the age at operation was ≥12 years, the patency rate at 10 years was 91.1% (n = 33), compared with 94.4% (n = 18) for patients <12 years old (Figure 3). When the age at operation was <12 years, the patency rate for ITA grafts in the later period was significantly higher than that in the early period ($P < .05$).

Degree of stenosis in grafted vessels

The number of coronary artery lesions in the grafted vessels in the 4 groups is shown in Table II. In a half of the total of 14 graft occlusions, the degree of stenosis in the grafted vessels was 50%. The number of 50% stenoses in the earlier and the later groups was as

Figure 4



Angiograms in a 6-year-old boy after PTBA for anastomotic stenosis. Left upper panel, Left coronary angiogram. Ninety percent localized stenosis in the LAD present before operation. Right upper panel, Angiogram 13 days postoperation. Internal thoracic artery graft stenosis was not detected. Left lower panel, Angiogram 3 months postoperation. The ITA graft stenosis was severe. Flow in the LAD through the ITA was decreased. Right lower panel, Angiogram 8 months postoperation. Anastomotic stenosis was improved. Good flow in the ITA is seen 4 months after PTBA.

follows: when the age at operation was ≥12 years, 3 (21%) and 1 (3%), respectively; when the age at operation was <12 years, 8 (27%) and 1 (6%), respectively. There were no significant differences between the groups. Both *P* values were .07.

Coronary artery bypass grafting was performed in 4 patients with 50% stenosis of the target vessels in the later period, and those grafts were occluded. These grafts were second grafts involving another target vessel that absolutely needed grafting.

Percutaneous transluminal balloon angioplasty for ITA graft stenosis

From 1999 onwards, PTBA for anastomotic stenosis in ITA graft was performed for 6 lesions in 6 patients, the grafted vessels being the LAD in 5 and the RCA in 1. The age at operation was <12 years in 5 of the 6 patients. The age at PTBA ranged from 4 to 16 years. The interval from operation to intervention ranged from 3 months to 1 year (median 4 months). One patient had a transient ST-T change during the procedure. The mean stenosis degree improved from 88% to 12%. The procedure prevented graft occlusion in all 6 patients and was associated with graft patency in the late period (Figure 3). There was no restenosis in all 6 patients on follow-up angiograms (Figure 4).

Discussion

In the group <12 years in the later period, the graft patency rate was similar to the older age group. In the younger age group, 5 lesions were successfully treated by PTBA. Without PTBA, the graft patency rate would be similar to the rate in the group <12 years in the early period of the present study or as previously reported.[1-3] Because vessel diameters are small in children, postoperative stenosis at the anastomotic site is likely to occur. This has a great influence on graft patency. Furthermore, competition with native coronary artery flow decreases the flow through the ITA, which encourages progressive

graft stenosis. Although the grafts were patent immediately after operation, the mentioned factors resulted in graft occlusion within several months after surgery. Patency of an ITA graft immediately after operation does not necessarily imply its long-term patency; its fate is decided within a few months postoperation. Percutaneous transluminal balloon angioplasty for the anastomotic site performed a few months after surgery helped prevent graft occlusion, and successful PTBA improved the graft patency rate in small children.[7-9]

In the group <12 years in the early period, 50% stenosis in the grafting vessels was frequently observed in the early period, and graft occlusion was common. We believe that graft occlusion is more likely to occur when the native coronary flow is preserved. The appropriate decision regarding CABG is critical. The existence of severe ischemia on examination and severe localized stenosis or complete occlusion is an absolute indicator for CABG. However, accurately determining the degree of localized stenosis in cases with giant aneurysms is often difficult; this difficulty may be further complicated by severely delayed flow.[10] In the middle 1980s, it was problematic to decide whether to recommend CABG for these patients. In many patients, ITA graft flow was compromised because of competition from the native LAD flow, and, as a result, prophylactic CABG failed to prevent myocardial damage. Therefore, indication for CABG has become strict since the 1990s in our hospital.

In the later period, additional second grafting for target vessels with <75% stenosis was ineffective. Most patients who have undergone CABG have multiple-vessel disease due to KD. Because future progression of stenosis in nongrafted native coronary arteries is probable, the other ITA should be preserved and not used for vessels that do not necessarily need grafting. Coronary revascularization should be performed only when the native flow is severely impaired. The results of coronary catheter intervention were reported to be satisfactory in young adults with coronary artery stenosis due to KD,[11] but there are few reports of coronary catheter intervention in children.[12] The number of choices of methods of coronary revascularization increases with physical growth, and delayed intervention, when appropriate, might bring better long-term results. Thus, the timing of coronary revascularization including CABG should be postponed until absolute indications develop and the patient is carefully followed-up, with frequent assessments of coronary blood flow reserve by echocardiography.

We believe that, in some respects, CABG is a better approach to coronary revascularization than catheter intervention for this population. If good flow in the ITA graft is established 1 year after surgery, long-term patency is virtually assured. The frequency of follow-up in the late period can be reduced after complete coronary revascularization by CABG, whereas after catheter intervention, close follow-up is needed to detect future restenosis of the target vessels.[12] Less frequent follow-up improves the patient's quality of life.[2] Potentially, it could ensure good coronary revascularization throughout one's life. Complete coronary revascularization by CABG might make it possible to discontinue long-term anticoagulant therapy in patients without persistent giant aneurysms or coronary artery lesions in other vessels.

Recently, evaluation of coronary artery lesions by 16-detector-row computed tomography in adults has been possible.[13,14] In our hospital, comparison of the findings with coronary angiogram by cardiac catheterization was good for anastomosis of the grafts in adolescents.[5] Sixteen-detector-row computed tomography and the detection of the ITA flow by 2-dimensional echocardiography have become the noninvasive methods to confirm the patency of the grafts. They have made possible less follow-up coronary angiogram by cardiac catheterization in adolescents and adults.

Conclusion

Appropriate indication of PTBA for anastomotic stenosis in ITA grafts greatly contributes to the patency of the grafts after KD in small children. Applying correct indications for CABG was very important for good patency of the grafts. Once good flow in the ITA 1 year after surgery is confirmed, graft patency will persist for >20 years.

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Hypertension

Association between cardiorespiratory fitness and prevalence of carotid atherosclerosis among men with hypertension

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Background Carotid atherosclerosis is a risk factor for cardiovascular mortality and may represent hypertension-related target organ damage. Cardiorespiratory fitness is inversely associated with cardiovascular mortality in hypertensive men. We tested the hypothesis that higher levels of cardiorespiratory fitness are inversely associated with the prevalence of carotid atherosclerosis in a cross-sectional study of 2532 (53.2 ± 8.5 years old) hypertensive men.

Methods Men with hypertension (defined as systolic over diastolic blood pressure of ≥140/90 mm Hg or self-reported use of antihypertensive medication) underwent maximal exercise treadmill testing with expired gas analysis. Carotid atherosclerosis was defined as stenosis of >25% and/or intima-media thickness of >1.2 mm using B-mode ultrasonography.

Results The overall prevalence of carotid atherosclerosis was 13.4%. The prevalence of carotid atherosclerosis was inversely associated with cardiorespiratory fitness category (low 22.5%, moderate 10.9%, and high 8.7%; $P < .001$ for trend). After adjusting for established risk factors, high and moderate fitness were associated with lower odds ratios for having carotid atherosclerosis, 0.63 (95% CI 0.47-0.85) and 0.62 (95% CI 0.41-0.92), respectively, compared with low fitness. Each metabolic equivalent increment higher peak oxygen uptake was associated with 11% (odds ratio 0.89, 95% CI 0.82-0.97) lower prevalence of carotid atherosclerosis.

Conclusions These results suggest that higher levels of cardiorespiratory fitness are inversely associated with the prevalence of carotid atherosclerosis in hypertensive men. (Am Heart J 2007;153:1001-5.)

Hypertension is a major risk factor for the development of atherosclerosis and for cardiovascular disease mortality.[1,2] Carotid atherosclerosis is one example of hypertension-related subclinical target organ damage[3,4] and is predictive of the risk of myocardial infarction or stroke in populations with and without hypertension.[5,6]

Epidemiological studies have shown that higher levels of cardiorespiratory fitness are associated with reduced risk of cardiovascular mortality in hypertensive patients.[7,8] Although an association between higher levels of cardiorespiratory fitness and low prevalence of carotid atherosclerosis in middle-aged men has been reported,[9-11] these relationships are not known in hypertensive subjects.

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Patients with hypertension have a substantially increased prevalence of type 2 diabetes.[12] Comorbid type 2 diabetes and hypertension is particularly damaging to the structure and function of the cardiac and vascular wall.[13] The risk of cardiovascular events is doubled in patients with both hypertension and type 2 diabetes compared with patients with isolated hypertension.[14] The association between cardiorespiratory fitness and carotid atherosclerosis in patients with both hypertension and type 2 diabetes is unknown.

Therefore, the objective of the present study was to test the hypothesis that higher levels of cardiorespiratory fitness using peak oxygen uptake (VO_2peak) are associated with a lower prevalence of carotid atherosclerosis in hypertensive men. We additionally investigated whether the association between cardiorespiratory fitness and carotid atherosclerosis is present in a subpopulation consisting of men with coexistence of diabetes.

Materials and methods

Subjects

Men who visited the Samsung Medical Center in Seoul, Korea, between January 2002 and March 2004 for routine

medical examinations were included in this study. These routine examinations were used for disease prevention/early detection purposes and consisted of a general physical examination, anthropometric measurements, blood pressure measurement, electrocardiography, blood analysis, carotid ultrasound, and an exercise stress test with concurrent metabolic gas analysis. From a total sample of 14 232 men, we excluded men with angina symptoms, abnormal electrocardiographic (ECG) changes during exercise stress testing (n = 712) or a diagnosis of coronary heart disease, and stroke. Our analysis sample included 2532 men with hypertension (53.2 ± 8.5 years old). Informed consent was obtained from all patients before health screening, and the study was approved by the medical center institutional review board.

All testing was completed in 1 visit. Information about antihypertensive medication use, oral hypoglycemic agent use, and cigarette smoking were obtained by a self-administered questionnaire. Hypertension was defined as a resting blood pressure of ≥140/90 mm Hg, self-reported physician-diagnosed hypertension, or self-reported use of antihypertensive medications. Diabetes was defined as a fasting glucose level of ≥126 mg/dL or self-reported use of an oral hypoglycemic agent.

Cardiorespiratory fitness

The graded exercise testing was conducted using a Bruce or modified Bruce protocol.[15] Expired gases were collected breath by breath using a 1-way valve and were analyzed using a metabolic cart (Jaeger Oxycon Delta, Wurtzberg, Germany). Peak oxygen uptake (mL/[kg · min]) and metabolic equivalents (METs, 1 MET = 3.5 mL/[kg · min] of oxygen uptake) were defined as the highest value recorded during the test. Exercise ECG was measured using 12-lead ECG (Q-4500, Quinton, Bothell, WA). The graded exercise testing was stopped for any of the following reasons: a rating of perceived exertion of >17 (Borg scale), achievement of >90% of age-predicted maximum heart rate (HR), extreme fatigue that interfered with the subject's ability to safely walk/run on the treadmill, systolic blood pressure (SBP) of >250 mm Hg, typical chest discomfort, severe arrhythmia, and >1 mm of ST-segment depression.

Carotid atherosclerosis

Carotid artery ultrasound imaging was performed using a high-resolution B-mode ultrasound system (Sonoline Antares, Siemens Medical System, Erlanger, Germany) with a 5 to 13 MHz linear array transducer. Intima-media thickness (IMT) was defined as the distance between the leading edge of the lumen-intima interface to the leading edge of the media-adventitia interface of the far wall of the carotid artery. All measurements were made at end diastole. The IMT of the common carotid artery was determined from an average of 5 measurements of a 10-mm segment (separated by 2-mm intervals) obtained 2 cm proximal to the carotid bifurcation. The IMT of the internal carotid artery was measured in the proximal 1 cm of the internal carotid artery. The overall maximal IMT was defined as the mean of the maximal IMT of both common carotid artery and internal carotid artery. An average IMT of >1.2 mm of the carotid arteries was considered indicative of carotid atherosclerosis.[16]

Stenosis of carotid arteries was defined by the degree of Doppler-derived peak systolic velocity (PSV) of the internal carotid artery and was categorized as no stenosis (0%-24%, ≤124 cm/s of PSV), mild stenosis (25%-49%, >125-149 cm/s of PSV), moderate stenosis (50%-70%, >150-174 cm/s of PSV), and severe stenosis (71%-99%, >175 cm/s of PSV). Carotid atherosclerosis was defined as stenosis of >25%[17] and/or IMT of >1.2 mm of the carotid arteries. The intraobserver coefficient of variation in our laboratory was 2.3%.

Other measurements

Resting SBP and diastolic blood pressure (DBP) was measured in the sitting position using an automated blood pressure monitor (Dinamap PRO 100, Milwaukee, WI) after at least 5 minutes of quiet rest. The lowest value of 2 measurements was used as resting blood pressure. Body mass index (BMI) was calculated as weight (kg) divided by height (m^2). Blood samples were collected after 12 hours of overnight fast and analyzed by the hospital clinical laboratory. Total cholesterol (TC), triglycerides, and high-density lipoprotein cholesterol (HDL-C) were analyzed enzymatically using a Hitachi 747 (Japan) analyzer. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. The white blood cell count (WBC) was determined using a quantitative automated hematology analyzer (Sysmex, Kobe, Japan). Fibrinogen was measured with the Clauss method using a CA-500 analyzer (Sysmex). Fasting glucose levels were determined using the glucose oxidase method (Hitachi 747, Tokyo, Japan). Inter- and intra-assay coefficients of variation were <5% for all blood variables.

Statistical analysis

Data are expressed as mean ± SD for continuous variables and counts and proportions for categorical variables. Two group comparisons were performed using independent t tests for continuous variables and a χ^2 test for categorical variables. First, we calculated and compared the prevalence of carotid atherosclerosis in each group using a χ^2 test. Next, multivariable logistic regression analyses were used to calculate odds ratios (OR) and 95% CIs of having atherosclerosis per increment higher MET score. To test for associations between carotid atherosclerosis and VO_2peak, subjects were divided into groups according to quartiles of VO_2peak. We classified the lowest fit as men in the bottom quartile of VO_2peak (<25%), moderate fitness as men in the 26th to 75th percentile, and the highest fit as the uppermost quartile based on published data from the KIHD Study.[18] We calculated ORs comparing the moderate and high-fit groups to the lowest fit. We investigated potential colinearity between values of lipids (r = 0.48-0.72, P < .001 with TC/HDL-C) and blood pressure (r = 0.64, P < .001 DBP and SBP). We then included the TC/HDL-C and SBP for these variables in the model. After conducting unadjusted linear or logistic regression (model 1), our multivariable modeling strategy was to adjust for age (model 2) and then for noncolinear cardiovascular risk factors (ie, age, smoking, BMI, SBP, antihypertensive medication, TC/HDL-C ratio, WBC, fibrinogen, HR, diabetes; model 3). We calculated trend tests for prevalence of carotid atherosclerosis by the 3 categories of cardiorespiratory fitness. We also conducted secondary analysis among men with diabetes to determine whether cardiorespiratory fitness was associated with carotid atherosclerosis in this subgroup. All tests for statistical significance were 2-sided. Statistical significance was set at P < .05 for all data. Statistical analyses were performed using the SPSS 12.0 (SPSS, Chicago, IL).

Table I. Clinical characteristics of hypertensive subjects with and without carotid atherosclerosis

Variables	Without carotid atherosclerosis (n = 2192)	With carotid atherosclerosis (n = 340)	P
Age (y)	52.6 ± 7.1	56.8 ± 6.3	<.001
BMI (kg/m^2)	25.3 ± 2.5	25.1 ± 2.5	.14
Smokers	448 (20.4)	76 (22.4)	.43
SBP (mm Hg)	136.8 ± 15.6	134.9 ± 17.4	.046
DBP (mm Hg)	87.8 ± 10.8	83.7 ± 11.5	<.001
Antihypertensive drugs	744 (33.9)	170 (50.0)	<.001
TC (mg/dL)	205.4 ± 33.9	205.5 ± 35.3	.96
HDL-C (mg/dL)	49.1 ± 11.5	46.5 ± 10.6	<.001
TC/HDL-C ratio	4.4 ± 1.1	4.6 ± 1.2	<.001
LDL-C (mg/dL)	136.8 ± 31.6	138.5 ± 32.3	.36
Triglyceride (mg/dL)	161.9 ± 99.3	156.2 ± 83.8	.31
Glucose (mg/dL)	102.9 ± 23.2	107.0 ± 25.0	.003
Diagnosed diabetes	393 (17.9)	114 (33.5)	<.001
WBC (×10^9 cells/L)	6.3 ± 1.6	6.3 ± 1.6	.83
Fibrinogen (mg/dL)	319.8 ± 74.6	314.2 ± 72.1	.20
HR (beat/min)	65.1 ± 10.5	63.4 ± 10.5	.005
Maximal HR (beat/min)	149.4 ± 14.9	141.5 ± 15.3	<.001
Maximal SBP (mm Hg)	189.1 ± 24.4	187.8 ± 27.1	.35
Exercise capacity (METs)	9.14 ±1.6	8.40 ± 1.7	<.001
Vo_2peak (mL/[kg · min])	31.9 ± 5.5	29.4 ± 6.0	<.001

Data are mean ± SD or number (percentage). *LDL-C*, Low-density lipoprotein cholesterol.

Results

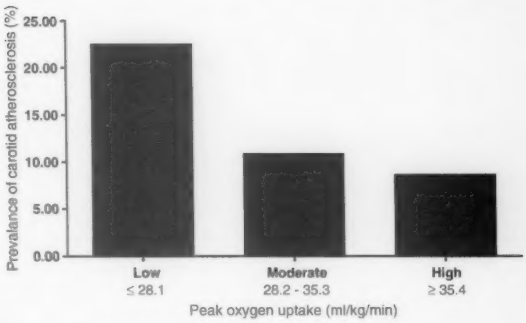
The prevalence of carotid atherosclerosis was 13.4% (n = 340). Subjects with carotid atherosclerosis were older on average; had higher TC/HDL-C ratio; higher glucose; diabetes; were taking antihypertensive drugs; and had lower SBP, DBP, HDL-C, resting HR, and Vo_2peak than subjects without carotid atherosclerosis (all $P < .05$) (Table I).

The Vo_2peak values corresponding with fitness categories are as follows: low, ≤28.1 mL/(kg · min) (n = 666); moderate, 28.2-35.3 mL/(kg · min) (n = 1271); and high, ≥35.4 mL/(kg · min) (n = 595). The prevalence of atherosclerosis was inversely associated with fitness (low 22.5%, moderate 10.9%, and high 8.7%; $P < .001$ for trend) (Figure 1).

In unadjusted logistic regression models, the OR of carotid atherosclerosis was 0.76 (95% CI 0.71-0.81, $P < .001$) per 1 MET change in Vo_2peak as a continuous variable. The METs were still significantly associated with carotid atherosclerosis (OR 0.89 [95% CI 0.82-0.97, $P < .008$] per 1 MET higher Vo_2peak) in multivariate logistic regression analysis (Table II).

Table III reports logistic regression analysis by groups of Vo_2peak. In an unadjusted model, subjects with high Vo_2peak were approximately 67% less likely to have carotid atherosclerosis than subjects in the low group ($P < .001$ for trend). After adjusting for established risk factors (age, smoking, BMI, SBP, antihypertensive medication, TC/HDL-C ratio, WBC, fibrinogen, HR, diabetes),

Figure 1



Prevalence of carotid atherosclerosis by fitness group ($P < .001$ for linear trend).

Table II. Logistic regression ORs (95% CI) for carotid atherosclerosis according to the METs and selected risk factors

Variables	OR	95% CI	P
METs*	0.89	0.82-0.97	.007
Smoking (yes/no)	1.14	0.84-1.55	.409
Age (y)	1.08	1.05-1.10	<.001
BMI (kg/m^2)	0.95	0.90-1.01	.063
SBP(mm Hg)	0.99	0.99-1.01	.539
TC/HDL-C ratio	1.20	1.08-1.34	.001
Diabetes (yes/no)	1.96	1.50-2.56	<.001
Antihypertensive medication (yes/no)	1.43	1.09-1.87	.010
WBC (×10^9 cells/L)	1.01	0.93-1.10	.807
Resting HR (beat/min)	0.99	0.97-0.99	.915
Fibrinogen (mg/dL)	0.99	0.99-1.00	.059

*Per 1 MET (3.5 mL/[kg · min]) higher Vo_2peak.

high and moderate fitness were each associated with significantly lower odds of having carotid atherosclerosis, 0.63 (95% CI 0.47-0.85) and 0.62 (95% CI 0.41-0.92), respectively, compared with low fitness ($P < .017$ for trend).

We conducted secondary analysis in the subset of subjects with diabetes (n = 507) to determine whether the association between fitness and atherosclerosis remained. The prevalence of carotid atherosclerosis was 22.5% (n = 114). The prevalence of atherosclerosis was significantly lower across incremental thirds of fitness (low 33.1%, moderate 19.6%, and high 12.8%; $P < .001$ for trend). Men in moderate or high fitness were significantly less likely to have carotid atherosclerosis than men in low fitness in the unadjusted model. This association was attenuated to nonsignificance with multivariable adjustment (Table IV). However, in further statistical analyses in the subgroup of men >50 years (n = 342), fitness was independently associated with preva-

Table III. Logistic regression ORs (95%CI) for carotid atherosclerosis by fitness group

Vo_2peak	High OR (95% CI)	Moderate OR (95% CI)	Low (Ref) 1.00	*P* for trend
Models				
Unadjusted	0.33 (0.24-0.46)	0.42 (0.33-0.54)	1.00	<.001
Age adjusted	0.60 (0.41-0.87)	0.64 (0.49-0.85)	1.00	.007
Multivariables adjusted	0.62 (0.41-0.92)	0.63 (0.47-0.85)	1.00	.017

Multivariables adjusted for age, smoking, BMI, SBP, antihypertensive medication, TC/HDL-C ratio, WBC, fibrinogen, HR, and diabetes.

Table IV. Logistic regression ORs (95% CI) for carotid atherosclerosis by fitness group in hypertension with type 2 diabetes

Peak oxygen uptake	High OR (95% CI)	Moderate OR (95% CI)	Low (Ref) 1.00	*P* for trend
Models				
Unadjusted	0.30 (0.15-0.61)	0.49 (0.31-0.78)	1.00	.001
Age adjusted	0.52 (0.24-1.13)	0.74 (0.44-1.22)	1.00	.09
Multivariables adjusted	0.54 (0.23-1.25)	0.76 (0.44-1.30)	1.00	.15

Multivariables adjusted for age, smoking, BMI, SBP, antihypertensive medication, TC/HDL-C ratio, glucose, WBC, fibrinogen, and HR. *Ref*, Reference.

lence of carotid atherosclerosis (OR 0.52, 95% CI 0.29-0.95, $P = .032$ high vs low fitness) (data not shown).

Discussion

In this cross-sectional study, we demonstrated that hypertensive men with higher levels of cardiorespiratory fitness were less likely to have carotid atherosclerosis. This relationship was independent of established risk factors. To the best of our knowledge, this is the first study to report that high levels of cardiorespiratory fitness are associated with lower prevalence of carotid atherosclerosis in hypertensive men.

Hypertension is clinically significant because of its association with cardiovascular mortality and morbidity as well as its association with target organ damage such as left ventricular hypertrophy and carotid atherosclerosis.[1,2] Controlling or preventing subclinical target organ damage can prevent further escalation of cardiovascular risk. Therefore, our findings are important because higher levels of cardiorespiratory fitness are associated with lower prevalence of carotid atherosclerosis in hypertension. Our results are consistent with previous reports noting an association between higher levels of cardiorespiratory fitness or physical activity and low prevalence of carotid atherosclerosis in middle-aged men.[9-11] We extend those findings by describing the same association in men with hypertension.

Because comorbid hypertension and diabetes is estimated to double the risk of cardiovascular events,[12-14] we conducted secondary analysis in a subset of patients with diabetes. As expected, the prevalence of carotid atherosclerosis in hypertensive men with type 2 diabetes was higher than in men with hypertension alone. Although the prevalence of carotid atherosclerosis was lower across incremental thirds of cardiorespiratory fitness, there was no statistically significant difference after adjusting for age and risk factors. Therefore, it is possible that the association between fitness and carotid atherosclerosis in hypertensive men with type 2 diabetes is related to older age. Further studies are needed to clarify the association between cardiorespiratory fitness and carotid atherosclerosis in this subset of high-risk subjects.

This study has several limitations. We cannot determine causation because of the cross-sectional nature of our study. We also did not control for diet status, including alcohol consumption. The effect of alcohol consumption or other dietary factors may potentially confound the relationship between cardiorespiratory fitness and carotid atherosclerosis.[19] Our sample included only men, so we are unable to determine whether this association extends to women. Also, cardiorespiratory fitness is not only determined by current activity level but also by genetics[15]; the proportion of fitness attributable to genetics is hypothesized as being relatively smaller than that proportion due to physical activity. Our database did not contain information about duration of hypertension and diabetes, so we were not able to account for this important measure of disease severity. C-reactive protein may be an important confounder in this relation but was not measured in this study. However, according to recent findings, C-reactive protein is not independently associated with carotid atherosclerosis.[20] Finally, our measurements of carotid atherosclerosis were used as a screening test and only assessed the presence or absence of increased carotid IMT or stenosis. Thus, carotid atherosclerosis could only be evaluated as a categorical variable, and we could not assess burden of atherosclerosis. One strength of this study is our use of directly measured VO_2peak as index of cardiorespiratory fitness.

In conclusion, these results suggest that higher levels of cardiorespiratory fitness are inversely associated with prevalence of carotid atherosclerosis in hypertensive men. However, future studies are needed to prospectively evaluate this association in population samples.

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Electrophysiology

Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation

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Background The Euro Heart Survey showed that antithrombotic treatment in patients with atrial fibrillation (AF) was moderately tailored to the 2001 American College of Cardiology, American Heart Association, and European Society of Cardiology (ACC/AHA/ESC) guidelines for the management of AF. What consequences does guideline-deviant antithrombotic treatment have in daily practice?

Methods In the Euro Heart Survey on AF (2003-2004), an observational study on AF care in European cardiology practices, information was available on baseline stroke risk profile and antithrombotic drug treatment and on cardiovascular events during 1-year follow-up. Antithrombotic guideline adherence is assessed according to the 2001 ACC/AHA/ESC guidelines. Multivariable logistic regression was performed to assess the association of guideline deviance with adverse outcome.

Results The effect of antithrombotic guideline deviance was analyzed exclusively in 3634 high-risk patients with AF because these composed the majority (89%) and because few cardiovascular events occurred in low-risk patients. Among high-risk patients, antithrombotic treatment was in agreement with the guidelines in 61% of patients, whereas 28% were undertreated and 11% overtreated. Compared to guideline adherence, undertreatment was associated with a higher chance of thromboembolism (odds ratio [OR], 1.97; 95% CI, 1.29-3.01; $P = .004$) and the combined end point of cardiovascular death, thromboembolism, or major bleeding (OR, 1.54; 95% CI, 1.14-2.10; $P = .024$). This increased risk was nonsignificant for the end point of stroke alone (OR, 1.42; 95% CI, 0.82-2.46; $P = .170$). Overtreatment was nonsignificantly associated with a higher risk for major bleeding (OR, 1.52; 95% CI, 0.76-3.02; $P = .405$).

Conclusions Antithrombotic undertreatment of high-risk patients with AF was associated with a worse cardiovascular prognosis during 1 year, whereas overtreatment was not associated with a higher chance for major bleeding. (Am Heart J 2007;153:1006-12.)

Prevention of stroke and thromboembolism (TE) is the vanguard of atrial fibrillation (AF) management. When compared with both placebo and antiplatelet agents, oral anticoagulation (OAC) effectively prevents TEs in patients at high risk for such an event.[1] In patients at low risk, an antiplatelet agent should suffice because the bleeding risk of OAC neutralizes the benefit of TE prevention in these patients.[2] Based on this evidence

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and on expert opinion, the 2001 joint ACC/AHA/ESC guidelines on AF management provided recommendations for thromboprophylaxis in AF.[3]

Despite the availability of trial evidence and guidelines, numerous observational studies have shown suboptimal application rates of OAC in clinical practice. The Euro Heart Survey recently reported that although the application rate of OAC has improved, antithrombotic drug therapy is only moderately tailored according to the risk classification scheme as proposed by the joint ACC/AHA/ESC guidelines.[4] Several factors are thought to underlie this discordance between guidelines and practice.

Regardless of the rationale behind management decisions, it is important to know the consequences lack of guideline adherence may have. Stroke and bleeding rates in observational studies have been shown to compare quite well with event rates in OAC-treated, high-risk patients of randomized controlled trials, although these studies were based on small populations and some had methodological limitations.[5,6] OAC efficacy in high-risk patients is just one aspect of guideline adherence in the whole spectrum of management of patients with AF, and the consequences of guideline deviance per se have not yet been addressed.

The aim of this report was to describe the consequences of guideline deviance in antithrombotic management from cardiology practices in a large European AF population. Our major questions were the following:

1. does undertreatment lead to an increased TE rate, and/or
2. does overtreatment cause avoidable bleedings?

Methods

In the Euro Heart Survey on AF (2003-2004), 5333 ambulant and hospitalized patients with AF were enrolled in cardiology practices. Details of the baseline survey have previously been described.[7] Patients were enrolled if they were 18 years or older and if they had an electrocardiogram or Holter recording showing AF during the qualifying admission/consultation or in the preceding 12 months. Patients with only atrial flutter on their electrocardiograms were excluded. Data were collected through the Internet and stored in a central database at the European Heart House. Data quality was verified by using automatic validation checks in the case report form and with additional edit checks by data monitors and the data analysis center. A follow-up was performed to assess mortality and incidence of major adverse events during 1 year.

For the purpose of this study, categorization of stroke risk and assessment of guideline adherence for antithrombotic therapy at baseline were assessed according to the ACC/AHA/ESC 2001 guidelines on AF management.[3]

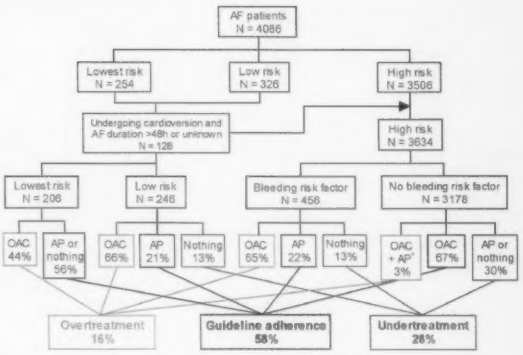
Stroke risk categorization

In a previous report we appointed patients to high-risk or highest risk groups to assess the influence of stroke risk on antithrombotic drug prescription.[4] For the present analysis, we combined these 2 groups together as high risk because both should receive OAC, and guideline adherence and deviance are similar. ***High risk*** is defined as the presence of at least one of the following factors: mitral stenosis, valve surgery, prior stroke/transient ischemic attack (TIA), age >75 years, heart failure or left ventricular ejection fraction ≤0.35, hypertension, or age ≥60 years in combination with diabetes mellitus or coronary artery disease (CAD). In addition, patients undergoing cardioversion (pharmacologic or electrical) when AF duration was >48 hours or unknown were also considered high risk.

Low risk is the absence of the above-mentioned high-risk factors, age ≥60 years, or age <60 years with other heart disease.

Lowest risk is defined as age <60 years and none of the above-mentioned risk factors (AF only).

Figure 1



Flow chart for categorizing antithrombotic guideline adherence. *In high-risk patients <60 years or =60 years without CAD and diabetes. *AP*, Antiplatelet agent.

Antithrombotic therapy guideline adherence

In high-risk patients without a bleeding risk factor (BRF)—a (prior) major bleeding, (prior) malignancy, or renal failure—OAC is recommended and, therefore, withholding OAC was considered to be undertreatment. In high-risk patients with at least one BRF, use of OAC was considered as overtreatment, use of an antiplatelet agent as appropriate, and no drug treatment as undertreatment. In high-risk patients aged ≥60 years and having either CAD or diabetes, an antiplatelet drug in combination with OAC is optional, and, therefore, all other high-risk patients receiving this combination were considered as overtreated. Low-risk patients should receive an antiplatelet drug, whereby prescribing OAC was considered to be overtreatment and no drug therapy as undertreatment. Finally, lowest risk patients should receive either an antiplatelet drug or no therapy, and therefore prescription of OAC was categorized as overtreatment.

Major adverse cardiovascular events

Major adverse events during follow-up were reported by the local data collectors according to the following definitions:

- Ischemic stroke: focal neurologic deficit of sudden onset as diagnosed by a neurologist, lasting longer than 24 hours and caused by ischemia.

Table I. Baseline characteristics of AF patients at high risk for stroke

	Undertreatment	Guideline followed	Overtreatment	P
No. of patients	1016	2214	404	
Age (y)	68 ± 12	68 ± 11	70 ± 12	.001
Female	44	43	41	.617
Valvular AF	4	16	17	<.001
Stroke/TIA	9	11	22	<.001
Other TE	1	4	4	.001
Heart failure	32	36	50	<.001
Hypertension	78	70	71	<.001
CAD	36	28	38	<.001
Diabetes mellitus	20	18	28	<.001
Peripheral vascular disease	7	7	18	<.001
COPD	14	12	22	<.001
SSS	4	5	10	<.001
Ventricular tachycardia	3	2	7	<.001
Ventricular fibrillation	1	1	2	.092
Bleeding risk				
Major bleeding	1	1	8	<.001
Malignancy	3	2	35	<.001
Renal failure	3	2	35	<.001
Strategy				<.001
Rhythm control	60	61	54	
Rate control	31	34	41	
None	9	5	5	
AF type				<.001
First detected	25	15	14	
Paroxysmal	42	22	22	
Persistent	13	28	21	
Permanent	21	35	44	
Other drugs				
ACE inhibitor	50	50	48	.750
AT II receptor blocker	13	14	17	.069
Diuretic	51	54	69	<.001
Dihydropyridin CCB	17	14	11	.005
β-Blocker	44	45	53	.017
Statin	21	26	32	<.001

ACE, Angiotensin-converting enzyme; *AT*, angiotensin; *CCB*, calcium-channel blocker.

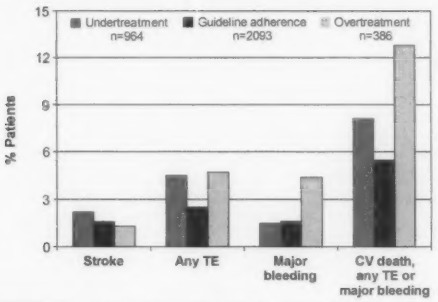
- Any TE: occurrence of ischemic stroke, myocardial infarction, pulmonary embolism, or peripheral embolism.
  - Myocardialinfarction: new or presumed new ST segment elevation in 2 or more continuous leads of 0.2 mV in leads V1, V2, or V3 and 0.1 mV in other leads and/or presumably new left bundle branch block and/or increase in cardiac enzyme level more than 2 times the upper values.
  - Peripheral embolism: embolism outside the heart, brain, eyes, and lungs.
- Major bleeding: either hemorrhagic stroke or another type of major bleeding.
  - Hemorrhagic stroke: focal neurologic deficit of sudden onset as diagnosed by a neurologist, lasting longer than 24 hours and caused by bleeding.
  - Other major bleeding: major bleeding other than hemorrhagic stroke requiring hospitalization and/or causing a decrease in hemoglobin level of more than 2 g/L and/or requiring blood transfusion.
- Cardiovascular death: death due to any cardiovascular reason such as myocardial infarction, heart failure, sudden cardiac death (all sudden deaths without any other known reason), stroke, or rupture of an aortic aneurysm.

Statistical analysis

Data analysis was performed with SPSS statistical software (release 12.01, SPSS Inc., Chicago, IL). Results in Table I are reported as mean ± standard deviation for age and as proportion within the column for the remaining variables. Multivariable logistic regression was performed to assess whether guideline adherence was independently associated with stroke, any TE, major bleeding, and the combined end point of cardiovascular death, any TE, and major bleeding during 1-year follow-up. Because the variable on antithrombotic guideline adherence was the central variable, it was kept in every final model regardless of its significance.

The following other variables were tested in these models: age, sex, hypertension, valvular AF (mitral stenosis or valve surgery), heart failure, prior ischemic stroke or TIA, prior TE, CAD, diabetes, prior major bleeding, prior minor bleeding, prior malignancy, renal failure, undergoing rate or rhythm control, chronic obstructive pulmonary disease (COPD), sick sinus

Figure 2



Absolute numbers of events				
Undertreatment	21	43	14	78
Guideline adherence	34	52	33	115
Overtreatment	5	18	17	49

Univariable absolute and proportional event rates during 1 year versus antithrombotic guideline adherence in patients at high risk for stroke. *CV*, Cardiovascular.

syndrome (SSS), prior ventricular tachycardia, prior ventricular fibrillation, and prescription of an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, diuretic, β-blocker, dihydropyridin calcium-channel blocker, and statin.

Variables were removed stepwise from the model when the *P* value exceeded .10. Variables with *P* value <.05 in the final model were considered to be significant contributors and were kept in the model. Hereafter, these models were validated by means of bootstrapping, which was performed with 100 samples for each reported multivariable logistic regression analysis. Bootstrapping provided information on the effect stability of each factor as a predictor of the outcome variable. Effects that were unstable were left out of the model stepwise, which eventually resulted in the final model with only stable significant associated factors, and these final models are reported here. For each variable in this final model the net odds ratio (OR) and its 95% CI, backward elimination log-likelihood χ^2 (−2 LL), degrees of freedom, and *P* value are reported. In addition, predictive accuracy of each model is reported as the area under the receiver operating characteristic (ROC) curve.

Results

In the initial survey, data on stroke risk profile and antithrombotic drug therapy at discharge were available for 5130 patients who were alive at the end of the baseline visit. Of these patients, survival status at 1-year follow-up was known for 4086 patients (80%). Compared with patients with complete follow-up data, patients for whom no follow-up data were available were enrolled more often at the cardiology ward (65% vs 54%; $P < .001$) instead of the outpatient clinic (21% vs 37%; $P < .001$), with a higher prevalence of heart failure (42% vs 32%; $P < .001$) and less treatment with OAC (54% vs 68%; $P < .001$).

Table II. Factors associated with stroke in patients at high risk for stroke

	OR (95% CI)	−2 LL	*df*	*P*
Antithrombotic guideline adherence		4	2	.170
Guideline followed	1 (Reference)			
Undertreatment	1.42 (0.82-2.46)			
Overtreatment	0.66 (0.29-1.49)			
Prior stroke/TIA	4.20 (2.44-6.94)	22	1	<.001

All variables that initially entered the multivariable analysis are summarized in the Methods section. Area under the ROC curve = 0.6445.

Antithrombotic therapy guideline adherence

Figure 1 shows that among patients with follow-up available, only 254 were classified as lowest and 326 as low risk, whereas the majority (n = 3506) was classified as high risk, according to the ACC/AHA/ESC guidelines. Among low(est)-risk patients, 128 underwent pharmacologic or electrical cardioversion when AF duration was either >48 hours or unknown. Because these patients should also receive OAC around the time of the cardioversion or at least at discharge in the acute setting, they were classified as high risk. The proportion with any BRF was clearly largest in high-risk (13%) compared with low-risk (3%) and lowest risk (2%) patients.

Antithrombotic guidelines were followed in 58% of the total population, whereas 26% were undertreated and only 16% were overtreated. Overtreatment mainly comprised 65% of high-risk patients with a BRF and receiving OAC; in addition, proportions of low-risk and lowest risk patients receiving OAC were remarkably high, 66% and 44%, respectively. The majority of undertreated patients were high-risk patients without a BRF in whom OAC was withheld.

Events in low(est) risk patients

During the 1-year follow-up, the only major events reported in lowest risk patients were 1 death associated with a myocardial infarction in a patient in whom the guideline was followed, and a noncardiovascular death in a patient that was overtreated. In low-risk patients, 1 undertreated patient died in association with a pulmonary embolism and 1 patient in whom the guideline was followed had an ischemic stroke. When low-risk patients were overtreated, 2 cardiovascular deaths were observed, of which 1 was in association with both an ischemic and a hemorrhagic stroke, and 1 ischemic stroke and 1 major bleeding other than a hemorrhagic stroke among the surviving patients.

Effect of antithrombotic guideline deviance in high-risk patients

Because of the relatively small sample size of patients at low(est) risk and the few observed major events in

Table III. Factors associated with any TE in patients at high risk for stroke

	OR (95% CI)	−2 LL	*df*	*P*
Antithrombotic guideline adherence		11	2	.004
Guideline followed	1 (Reference)			
Undertreatment	1.97 (1.29-3.01)			
Overtreatment	0.85 (0.42-1.74)			
Peripheral vascular disease	2.15 (1.28-3.64)	7	1	.006
Prior stroke/TIA	1.91 (1.17-3.11)	6	1	.013
Renal failure	2.48 (1.24-4.99)	6	1	.015
Prior other TE	2.66 (1.26-5.61)	5	1	.020
CAD	1.61 (1.08-2.39)	5	1	.020

All variables that initially entered the multivariable analysis are summarized in the Methods section. Area under the ROC curve = 0.6933.

Table IV. Factors associated with major bleeding in patients at high risk for stroke

	OR (95% CI)	−2 LL	*df*	*P*
Antithrombotic guideline adherence		2	2	.405
Guideline followed	1 (Reference)			
Undertreatment	0.89 (0.47-1.69)			
Overtreatment	1.52 (0.76-3.02)			
Prior major bleeding	7.31 (3.28-16.27)	19	1	<.001
Prior minor bleeding	4.10 (1.78-9.51)	8	1	.004
Age, per year increase	1.03 (1.01-1.06)	7	1	.010

All variables that initially entered the multivariable analysis are summarized in the Methods section. Area under the ROC curve = 0.6851.

this subgroup, we chose to focus on the 3634 patients at high risk for stroke. Within this subgroup the guidelines were followed in 2093 (61%) patients, 964 (28%) were undertreated, and 386 (11%) were overtreated. Overtreated patients were oldest and frequently had a (prior) stroke or TIA, heart failure, diabetes, peripheral vascular disease, COPD, SSS, ventricular tachycardia, and potential BRFs (Table I). They also less frequently underwent a rhythm control strategy, more often had permanent AF and more often received a diuretic or statin. In comparison with the guideline-adherent group, undertreated patients less often had valvular AF, and more often hypertension, CAD, and first detected or paroxysmal AF.

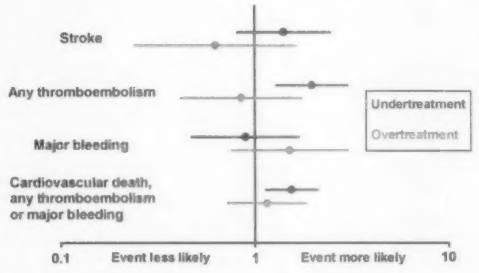
Crude (unadjusted) incidence among high-risk patients of major bleeding, cardiovascular death, and the combined end point of cardiovascular death, any TE, and major bleeding was highest in overtreated patients (Figure 2). Compared with the guideline-adherent group, any TE and the combined end point were more frequently observed in the undertreated group. Incidence of ischemic stroke slightly decreased from undertreatment to overtreatment. Of 64 major bleedings, only 8 were intracranial hemorrhages (ICH),

Table V. Factors associated with combined end point of cardiovascular death, any TE, and major bleeding in patients at high risk for stroke

	OR (95% CI)	−2 LL	*df*	*P*
Antithrombotic guideline adherence		7	2	.024
Guideline followed	1 (Reference)			
Undertreatment	1.54 (1.14-2.10)			
Overtreatment	1.15 (0.72-1.84)			
Heart failure	2.03 (1.54-2.67)	25	1	<.001
Age, per year increase	1.03 (1.01-1.04)	14	1	<.001
Peripheral vascular disease	2.20 (1.52-3.18)	16	1	<.001
Prior major bleeding	3.59 (1.98-6.51)	16	1	<.001
Renal failure	1.80 (1.11-2.93)	5	1	.020

All variables that initially entered the multivariable analysis are summarized in the Methods section. Area under the ROC curve = 0.6881.

Figure 3



Multivariable effect of antithrombotic guideline deviance on 1-year outcome. Results are reported as OR with 95% CI compared with the reference group "guideline adherence" (OR, 1).

with comparable low proportions in undertreatment (0.1%), guideline followed (0.4%), and overtreatment (0.3%).

Tables II through V show results of multivariable logistic regression on factors associated with the occurrence of stroke, any TE, major bleeding, and the combined end point of cardiovascular death, any TE, and major bleeding. The effect of under- and overtreatment in these 4 analyses is also visualized in Figure 3. Compared to guideline adherence, undertreatment showed a trend toward a higher risk, and overtreatment toward a lower risk for stroke, although both were nonsignificant. Occurrence of stroke seemed most likely with a prior stroke/TIA (Table II). Clearly significant was the association of undertreatment with an increased risk for any TE because it was the strongest associated factor in this model (Table III). Guideline adherence and undertreatment showed a

similar risk for major bleeding, but overtreatment did show a nonsignificant trend toward a higher risk for a major bleeding. Major bleeding was most likely to occur in patients with prior bleedings and with high age (Table IV). When combining any TE and major bleeding and adding cardiovascular death to the end point, undertreatment was associated with a significant higher risk for one of these events. Concomitant pathologies had the strongest association with occurrence of this combined end point (Table V).

Discussion

The Euro Heart Survey on AF is the first observational study to show that antithrombotic undertreatment is associated with worse cardiovascular outcome compared to guideline adherence. Overtreatment was not associated with a significant increase in bleeding risk.

Effect of antithrombotic guideline deviance in daily practice

In the Euro Heart Survey, most of the patients were at high risk for stroke. Because more of these patients were undertreated than overtreated, undertreatment of high-risk patients seems to be the main problem when analyzing guideline-deviant antithrombotic management in AF. This holds especially true because undertreatment led to an adverse outcome compared to guideline adherence, whereas overtreatment did not. Previous observational studies have shown that OAC is beneficial in clinical practice patients, and that stroke and bleeding rates of randomized controlled trials translate well into daily practice.[5,6] Because denying OAC in eligible patients constituted the main bulk of undertreatment, this survey indirectly demonstrates OAC efficacy in clinical practice.

Above all, this analysis is the first to show that global undertreatment—as defined by the guidelines—was associated with a worse cardiovascular outcome compared to guideline adherence. On the other hand, overtreatment of high-risk patients was not associated with an increased bleeding risk compared with guideline-adherent treatment. Of note, overtreatment with OAC of low(est)-risk patients hardly led to a marked increase in bleeding events. In agreement with previous findings, our results imply that when deciding on antithrombotic treatment, bleeding risk is subordinate to stroke risk, and that being conservative by withholding appropriate antithrombotic treatment is more harmful than treating patients aggressively.[8]

Weighing the risk for stroke and bleeding to tailor antithrombotic treatment in AF

Because overtreatment is not associated with a marked excess in bleeding, although the protective effect—as expected—is retained, this suggests that the concept of overtreatment as defined by the guidelines is not completely appropriate in real-life clinical practice. This perhaps encompasses too many clinical situations in which a more aggressive antithrombotic treatment may be justified. For example, our results show that patients with a prior stroke or TIA, irrespective of whether antithrombotic management follows the guidelines or not, have a high risk for stroke recurrence. Taken together, a more aggressive approach may be warranted in these patients, possibly by aiming at higher international normalized ratio (INR) levels (2.5-3.5) or adding an antiplatelet agent, such as those observed from recent data obtained by adding the antiplatelet agent triflusal to acenocoumarol, in high-risk patients with AF.[9]

Overrating the concept of overtreatment probably relates to the fact that the importance of classic BRFs is exaggerated.[10,11] Gage et al recently published the $HEMORR_2HAGES$ scheme, which identified risk factors for any major bleeding.[12] In patients with AF, however, OAC-induced ICH is the natural counterpart of ischemic stroke. Although the incidence of ICH is very low, even in randomized clinical trials,[13] its consequences are more devastating than the consequences of major extracranial bleeding. Other major bleedings may be amenable to local management, and in specific cases when bleeding risks are available, a secondary decision to stop or not start OAC or the combination of OAC and aspirin may be taken. Therefore, it seems most important to consider mainly ICH risk when performing a risk-benefit assessment for appropriate antithrombotic treatment application.

Prior ischemic stroke, high age, and high INR values (>4.0) are associated with increased ICH risk.[14,15] However, risk for stroke is much higher than ICH risk in the elderly and in patients with a prior ischemic stroke.[13] In addition, aiming toward evidence-based INR ranges (2.0-3.0) should not lead to patients spending a large proportion of the time in relatively unsafe INR levels above 4.0.[16,17] Considering the above, these classic ICH risk factors should not be a reason to withhold OAC. It has to be mentioned that aiming at INR <2.0 does not lead to fewer bleedings, especially in elderly patients, but does lead to increased stroke rates.[14,18,19] We therefore suggest that we should consider only patients with a known or perceived (extreme) high risk for ICH, with recurrence of another type of uncontrollable major bleeding or with specific bleeding disorders, for exclusion from OAC use.

Strengths

The Euro Heart Survey provides a unique insight into the consequences of antithrombotic guideline deviance—rather than exclusively OAC efficacy—in the total AF spectrum as seen in European cardiology practice.

Limitations

We might underestimate the magnitude of the effects of both under- and overtreatment because more severely diseased patients dropped out of the follow-up and because our follow-up was restricted to 1 year during which few strokes and bleedings occurred. Information was available on prior major bleeding, prior malignancy, and renal failure as potential contraindications for OAC, but not for other potential contraindications for any major bleeding. We do not know whether patients received the same antithrombotic drug as that given at discharge during the entire duration of the follow-up period. Finally, we did not have information on quality of INR control for patients on OAC.

Clinical implications

These results stress the importance of antithrombotic therapy guideline implementation in patients with AF especially to prevent undertreatment of patients at high risk for stroke. Based on our results, one might expect that low(est)-risk patients do not seem to bleed excessively on OAC, and by starting OAC the patient is protected against stroke and TE should there be risk factors that are currently undetected or that will develop in the future. Whether physicians have to focus on risks for any major bleeding or specifically ICH when performing a risk-benefit assessment for appropriate antithrombotic treatment should be discussed.

Central data collection was done at the European Heart House of the European Society of Cardiology, Sophia Antipolis, France. Data analysis was done at the Department of Cardiology, University Hospital Maastricht, Maastricht, the Netherlands. We thank the Euro Heart Survey team, national coordinators, investigators, and data collection officers for performing the survey.

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Imaging and Diagnostic Testing

Prognostic role of transesophageal echocardiography in acute type A aortic dissection

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Background Acute type A aortic dissection (AAD) remains a highly lethal entity for which emergent surgical correction is standard care. Prior studies have identified specific clinical findings as being predictive of outcome. The prognostic significance of specific findings on imaging studies is less well described. We sought to identify the prognostic value of transesophageal echocardiography (TEE) in medically and surgically treated patients with AAD.

Methods We studied 522 AAD patients enrolled over 6 years in the International Registry of Acute Aortic Dissection who underwent TEE. Multivariate analysis identified independent associations of inhospital mortality, first using clinical variables (model 1), after which TEE data were added to build a final model (model 2).

Results Inhospital mortality was 28.7%. Transesophageal echocardiographic evidences of pericardial effusion (P = .04), tamponade (P < .01), periaortic hematoma (P = .02), and patent false lumen (P = .08) were more frequent in nonsurvivors. Dilated ascending aorta (P = .03), dissection localized to the ascending aorta (P = .02), and thrombosed false lumen (P = .08) were less common in nonsurvivors. Model 1 identified age ≥70 years, any pulse deficit, renal failure, and hypotension/shock as independent predictors of death. Model 2 identified dissection flap confined to ascending aorta (odds ratio 0.2, 95% CI 0.1-0.6) and complete thrombosis of false lumen (odds ratio 0.15, 95% CI 0.03-0.86) as protective. In the medically treated group, mortality was 31% for subjects with a partially or completely thrombosed false lumen versus 66% in the presence of a patent false lumen.

Conclusions Transesophageal echocardiography provides prognostic information in AAD beyond that provided by clinical risk variables. (Am Heart J 2007;153:1013-20.)

Despite recent advances in diagnostic and therapeutic techniques, acute type A aortic dissection (AAD) remains associated with high morbidity and mortality.[1-8] Transesophageal echocardiography (TEE) is a versatile and accurate diagnostic tool for evaluating patients with known or suspected AAD.[9-17] Our previous analysis identified the prognostic value of the clinical variables (age ≥70 years, any pulse deficit, renal failure, hypotension/shock/tamponade, abrupt onset of chest pain, and electrocardiographic [ECG] evidence of ischemia) to predict inhospital death in AAD.[3] The prognostic role of TEE above and beyond that provided by clinical risk factors in AAD patients is not known. The purpose of this study was to identify the prognostic value of TEE in medically and surgically treated AAD.

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Methods

The inception and structure of the International Registry of Acute Aortic Dissection (IRAD) have been described previously.[2] In brief, 18 large referral centers in 8 countries agreed to participate in the ongoing registry. Beginning January 1, 1996, consecutive patients with AAD (both type A and type B) presenting to IRAD sites were enrolled. Patients were identified prospectively at presentation or retrospectively by

Table I. Demographics, clinical presentation, complications, and TEE findings for the total study population

Variable	Overall	Survived	Died	P
n (%)	522 (100)	372 (71.3)	150 (28.7)	
Demographics				
Age (y), mean (±SD)	61.2 (14.3)	60.3 (13.6)	63.5 (15.7)	.02
Age ≥70 y (%)	170 (32.6)	108 (29.0)	62 (41.3)	.007
Patients' history				
Marfan syndrome (%)	31 (6.2)	22 (6.0)	9 (6.4)	.87
Hypertension (%)	332 (65.9)	241 (66.6)	91 (64.1)	.60
Clinical presentations and signs				
Migrating pain (%)	66 (13.6)	39 (11.3)	27 (19.0)	.02
All neurological deficits (%)	84 (16.2)	52 (14.0)	32 (21.6)	.03
Coma/Altered consciousness (%)	66 (13.2)	31 (8.7)	35 (24.5)	<.001
Systolic BP (mm Hg), mean (±SD)	127.2 (38.0)	131.7 (35.6)	116.0 (41.7)	<.001
Hypotension/Shock (%)	141 (28.2)	72 (20.2)	69 (47.9)	<.001
Any pulse deficit (%)	135 (29.5)	81 (25.0)	54 (40.6)	.001
Inhospital complications				
All neurological deficits (%)	138 (27.8)	83 (22.9)	55 (41.0)	<.001
Coma/Altered consciousness (%)	31 (6.8)	6 (1.8)	25 (29.5)	<.001
Myocardial ischemia (%)	61 (12.3)	37 (10.4)	24 (17.3)	.04
Mesenteric ischemia/infarction (%)	27 (5.5)	10 (2.8)	17 (12.1)	<.001
Acute renal failure (%)	95 (19.3)	47 (13.2)	48 (34.8)	<.001
Hypotension (%)	166 (33.5)	78 (21.9)	88 (63.3)	<.001
Cardiac tamponade (%)	88 (17.8)	40 (11.3)	48 (34.5)	<.001
Limb ischemia (%)	59 (12.1)	32 (9.1)	27 (19.9)	.001
TEE findings				
Aneurysm (%)	120 (26.6)	95 (29.5)	25 (19.4)	.03
Intramural hematoma (%)	62 (13.9)	41 (12.8)	21 (16.5)	.30
Dissection flap or hematoma extends to:				
Ascending aorta (%)	80 (23.6)	64 (27.4)	16 (15.2)	.02
Arch (%)	83 (24.5)	55 (23.5)	28 (26.7)	.53
Descending aorta (%)	165 (48.7)	106 (45.3)	59 (56.2)	.06
False lumen patency				
Patent (%)	247 (74.4)	170 (71.7)	77 (81.1)	.08
Partial thrombosis (%)	57 (17.2)	43 (18.1)	14 (14.7)	.46
Complete thrombosis (%)	28 (8.4)	24 (10.1)	4 (4.2)	.08
Distal communication (%)	40 (10.8)	27 (10.4)	13 (11.8)	.69
Site of intimal tear				
Ascending aorta (%)	205 (49.5)	154 (52.9)	51 (41.5)	.03
Arch (%)	22 (5.3)	16 (5.5)	6 (4.9)	.80
Descending (%)	10 (2.4)	7 (2.4)	3 (2.4)	>.99
Multiple (%)	10 (2.4)	7 (2.4)	3 (2.4)	>.99
PEF (%)	209 (43.8)	139 (40.9)	70 (51.1)	.04
Periaortic hematoma (%)	75 (17.3)	45 (14.7)	30 (23.8)	.02

BP, Blood pressure; *PEF*, pericardial effusion.

searching hospital discharge diagnosis records and/or surgical and echocardiography databases. Diagnosis was suspected on the basis of the history and physical examination and was confirmed by an imaging study, visualization at surgery, and/or postmortem examination.

A standard questionnaire was used to collect data on each patient including demographics, medical history, clinical presentations, physical findings, imaging results, details of medical and surgical management, and outcome. Completed data entry forms were forwarded to the coordinating center at the University of Michigan for analysis. Chart review was used to document inhospital clinical events and inhospital mortality. Standard American College of Cardiology/American Heart Association definitions were used to define inhospital complications.[18]

All patients with AAD enrolled in IRAD (from January 1, 1996, to October 31, 2001) who underwent TEE were included in the current analysis. *Acute type A aortic dissection* was defined as any dissection that involved the ascending aorta and/or the aortic arch, irrespective of distal involvement, with symptom onset within 14 days of diagnosis. Traumatic dissection was excluded but intramural hematoma was included in the IRAD database.

Statistical analysis

Summary statistics are presented as frequencies and percentages or as mean ± SD. Missing data were not defaulted to negative, and denominators reflect only reported cases. Associations of death among nominal variables were compared using χ^2 test and 2-sided

Table II. Transesophageal echocardiographic findings in surgically treated patients

TEE results	Overall (n = 434*)	%	Alive (n = 328*)	%	Dead (n = 106*)	%	P
Normal	5	2.0%	5	1.7%	0	0.0%	.34
Aneurysm	104	27.8%	86	30.3%	18	20.0%	.06
Intramural hematoma	9	2.3%	5	1.7%	4	4.2%	.24
Site of origin of dissection							
Aortic root	151	39.8%	115	40.5%	36	37.9%	.65
Sinotubular junction	71	18.7%	54	19.0%	17	17.9%	.81
Ascending	140	36.9%	104	36.6%	36	37.9%	.82
Arch	11	2.9%	7	2.5%	4	4.2%	.48
Left subclavian level	2	0.5%	2	0.7%	0	0.0%	>.99
Descending	2	0.5%	1	0.4%	1	1.1%	.44
Dissection flap or hematoma extends to:							
Ascending aorta	69	24.6%	56	27.2%	13	17.3%	.09
Arch	71	25.3%	52	25.2%	19	25.3%	.99
Left subclavian level	10	3.6%	8	3.9%	2	2.7%	>.99
Descending	130	46.3%	89	43.2%	41	54.7%	.09
False lumen patency							
Patent	217	78.6%	160	76.6%	57	85.1%	.14
Partial thrombosis	40	14.5%	32	15.3%	8	11.9%	.50
Complete thrombosis	19	6.9%	17	8.1%	2	3.0%	.18
Distal communication	35	11.4%	25	11.0%	10	12.3%	.75
Arch vessel involvement	53	16.8%	42	17.9%	11	13.4%	.34
Site of intimal tear							
Ascending aorta	189	53.4%	148	55.8%	41	46.1%	.11
Arch	18	5.1%	13	4.9%	5	5.6%	.78
Descending	8	2.3%	5	1.9%	3	3.4%	.42
Multiple	6	1.7%	5	1.9%	1	1.1%	>.99
PEF	177	45.0%	129	43.4%	48	50.0%	.26
Periaortic hematoma	60	17.0%	38	14.3%	22	25.3%	.02
Aortic regurgitation	285	69.9%	217	70.2%	68	68.7%	.77
Coronary arteries compromised	28	8.6%	21	8.4%	7	9.2%	.82
PEF w/ tamponade as sign of preoperative complication	59	13.6%	36	11.0%	23	21.7%	.005

*Denominators reflect only cases reported, and missing data are not defaulted to zero.

Fisher exact test. Continuous univariate predictors for death were tested using *t* test or Wilcoxon-Mann-Whitney test as appropriate.

For sensitivity measurements, analysis was limited to the event variables found in the data form: normal, abnormal/indeterminate, aneurysm, dissection, intimal flap, and intramural hematoma. The analysis included only initial images to avoid confounding information from sequential imaging studies. Reports without the event details "normal" through "intramural hematoma"; but having anatomical details such as site, patency, distal communication, and the like rarely occurred. When such event variables were missing, these images were not included in the sensitivity analysis.

Predictive modeling

Multivariate logistic regression analysis was used to identify independent associations of inhospital mortality, first using only demographic and clinical variables found to have marginal association ($P < .20$) with inhospital death on univariate testing (model 1). The TEE information was then added to build model 2. Diagnostic routines (the Hosmer-Lemeshow test for lack of fit and likelihood ratio test) were used for the final model selection. The c-index was calculated to evaluate model discrimination. For all analyses, SAS Version 8.2 (SAS Institute, Cary, NC) was used. The TEE and clinical data were first analyzed for the total cohort and then separately for the medically and surgically treated cohorts.

Results

Select demographics, medical history, clinical presentation, and TEE findings of the study subjects are described in Table I. Of 1078 patient enrolled in the IRAD registry, 675 (63%) patients had AAD and 522 (77.3%) underwent TEE. Mean age was 61.2 ± 14.3 years with 32.6% being ≥70 years. Transesophageal echocardiography was performed as the first imaging study in 276 patients (54.4%) and as the second study in 222 (43.8%). The most frequent preexisting risk factors for AAD were hypertension (65.9%), atherosclerosis (26.8%), and prior cardiac surgery (16.0%). An abrupt onset of pain was the most common presenting symptom and was reported by 84.6% of subjects. Inhospital death occurred in 150 patients (28.7%). Inhospital complications were more prevalent among

Table III. Transesophageal echocardiographic findings in medically treated patients

TEE results	Overall (n = 88*)	%	Alive (n = 44*)	%	Dead (n = 44*)	%	P
Normal	1	1.3%	1	2.6%	0	0.0%	.49
Abnormal/Indeterminate	54	66.7%	26	65.0%	28	68.3%	.75
Aneurysm	16	20.8%	9	23.7%	7	17.9%	.54
Intramural hematoma	8	10.4%	5	13.5%	3	7.5%	.47
Site of origin of dissection							
Aortic root	24	30.8%	10	26.3%	14	35.0%	.41
Sinotubular junction	7	9.0%	2	5.3%	5	12.5%	.43
Ascending	29	37.2%	12	31.6%	17	42.5%	.32
Arch	17	21.8%	13	34.2%	4	10.0%	.01
Left subclavian level	0	0.0%	0	0.0%	0	0.0%	–
Descending	1	1.3%	1	2.6%	0	0.0%	.49
Dissection flap or hematoma extends to:							
Ascending aorta	11	19.0%	8	28.6%	3	10.0%	.07
Arch	12	20.7%	3	10.7%	9	30.0%	.07
Left subclavian level	0	0.0%	0	0.0%	0	0.0%	–
Descending	35	60.3%	17	60.7%	18	60.0%	.96
False lumen patency							.131
Patent	30	53.6%	10	35.7%	20	71.4%	.007
Partial thrombosis	17	30.4%	11	39.3%	6	21.4%	.15
Complete thrombosis	9	16.1%	7	25.0%	2	7.1%	.14
Distal communication	5	8.2%	2	6.3%	3	10.3%	.66
Arch vessel involvement	9	14.1%	4	12.9%	5	15.2%	>.99
Site of intimal tear							
Ascending aorta	16	26.7%	6	23.1%	10	29.4%	.58
Arch	4	6.7%	3	11.5%	1	2.9%	.31
Descending	2	3.3%	2	7.7%	0	0.0%	.18
Multiple	4	6.7%	2	7.7%	2	5.9%	>.99
Periaortic hematoma	15	18.8%	7	17.1%	8	20.5%	.69
Aortic regurgitation	38	45.8%	21	50.0%	17	41.5%	.44
Coronary arteries compromised	4	5.7%	0	0.0%	4	12.1%	.05
PEF w/ tamponade as sign of AAD	2	2.3%	0	0.0%	2	4.7%	.24
PEF w/ tamponade as sign of complication	13	14.8%	2	4.5%	11	25.0%	.007

*Denominators reflect only cases reported, and missing data are not defaulted to zero. AAD, Acute aortic dissection.

patients who ultimately died versus those who survived (Table I). Most patients (83.1%) underwent surgery for repair of AAD (inhospital mortality 24.4%). Some required aortic valve replacement (23.6%) or coronary bypass surgery (16.1%). In the 16.9% who were treated medically (inhospital mortality 50%), reasons for not having surgery mainly included advanced age (20%), excessive comorbidity (68%), and patient refusal (19%). For the entire group, TEE evidences of pericardial effusion ($P = .04$), cardiac tamponade ($P < .01$), periaortic hematoma ($P = .02$), and patent false lumen ($P = .08$) were more frequent in nonsurvivors (Table I). A dilated ascending aorta ($P = .03$), dissection confined to the ascending aorta ($P = .02$), and completely thrombosed false lumen ($P = .08$) were less common in nonsurvivors.

For the 434 patients undergoing surgical repair (Table II), preexisting aneurysm (30.3% vs 20%, $P = .06$) and dissection confined to the ascending aorta (27.2% vs 17.3%, $P = .09$) were more common in survivors. Periaortic hematoma (25.3% vs 14.3%, $P = .02$) and pericardial effusion with tamponade were more prevalent in nonsurvivors (11.7% vs 5%, $P = .02$). False lumen patency was not a predictor of mortality in the surgical subgroup.

For the subgroup of 88 medically treated patients (Table III), false lumen patency was significantly more frequent in those who died than in those who survived (71.4% vs 35.7%, $P = .007$), whereas both partial and complete thromboses were more prevalent in survivors. A dissection flap confined to the ascending aorta was seen in 28.6% of survivors and only 10% of those who died ($P = .07$). Pericardial effusion with tamponade remained a univariate predictor of mortality ($P = .007$) in the nonsurgical group.

For the entire population, model 1 identified age ≥70 years, any pulse deficit, renal failure, and hypotension/shock as independent predictors of death (with abrupt onset of pain and abnormal presenting ECG showing a trend). Model 2, which added TEE data, identified cardiac tamponade as being independently associated with death (odds ratio [OR] 2.7, 95% CI 1.1-6.5), whereas dissection flap confined to ascending aorta (OR 0.2, 95% CI 0.1-0.6) and false lumen thrombosis (OR 0.15, 95% CI 0.03-0.86) were protective. Age, renal failure, and abnormal ECG lost

Table IV. Prediction models with clinical and TEE variables for type A surgical patients

Model variables	Overall surgical type A %	% Among survivors	% Among deaths	Parameter coefficient	P	Death, OR (95% CI)
Model 1: clinical variables only (c-index 0.80)						
Age ≥70 y	27.6	25.6	34.0	0.37	.26	1.45 (0.76-2.76)
Male sex	71.2	73.5	64.2	0.42	.22	1.52 (0.78-2.96)
History AVR	4.4	2.6	10.2	2.15	.0002	8.58 (2.77-26.62)
Migrating pain	13.8	11.5	21.0	1.42	.0003	4,15 (1.92-8.99)
Presenting hypotension/shock	28.5	21.3	51.0	1.36	<.0001	3.90 (2.04-7.46)
Any pulse deficit	30.3	26.0	44.0	0.81	.01	2.26 (1.21-4.21)
Preoperative tamponade	15.6	11.1	29.7	1.23	.001	3.42 (1.63-7.16)
Model 2: clinical variables (c-index 0.83)						
Age ≥70 y	27.6	25.6	34.0	0.56	.14	1.76 (0.84-3.69)
Male sex	71.2	73.5	64.2	0.24	.53	1.27 (0.60-2.71)
History AVR	4.4	2.6	1.2	2.49	.0004	12.02 (3.07-46.97)
Presenting hypotension/shock	28.5	21.3	51.0	1.32	.0005	3.75 (1.77-7.94)
Migrating pain	13.8	11.5	21.0	2.17	<.0001	8.76 (3.43-22.39)
Any pulse deficit	30.3	26.0	44.0	0.84	.02	2.33 (1.16-4.69)
Preoperative tamponade	15.6	11.1	29.7	1.36	.002	3.90 (1.65-9.22)
TEE variables						
Periaortic hematoma	17.0	14.3	25.3	0.95	.04	2.59 (1.06-6.32)

AVR, Aortic valve replacement.

their significance as predictors of death in model 2. The addition of TEE information improved the discriminatory power of the prediction model (c-index: model 1 = 0.74, model 2 = 0.78).

Model 1 and model 2 predictors of outcome for surgically treated AAD patients are presented in Table IV. Multivariable predictors included presenting with hypotension or shock, migrating pain, any pulse deficit, and preoperative cardiac tamponade. Model 2, which incorporated TEE variables, additionally identified periaortic hematoma on TEE as an independent predictor of mortality. When only the surgically treated patients were considered, false lumen patency and extent of dissection lost their discriminatory value.

For the medially treated subset, model 1 identified age, coma or altered mental status, and presenting hypotension or shock as independent predictors (Table V). The addition of TEE variables in model 2 identified false lumen patency as an independent predictor (OR 10.65, $P = .007$). In the medically treated subset, a patent false lumen was noted in 30 patients, 20 of whom died. Inhospital mortality was 22.2% (2 of 9) in medically treated patients with complete thrombosis and 35.3% (6 of 17) in those with partial thrombosis. Survival was 69% if either complete or partial thrombosis was present.

Discussions

Acute type A aortic dissection is a highly lethal entity with early mortality approaching 1% per hour and 30-day mortality reported to be as high as 75% to 90%.[5,6] The clinician must have a high index of suspicion in view of the frequently atypical symptoms.[2,16,17] Because of the high early mortality of AAD, cardiovascular imaging techniques are an essential part of the diagnostic strategy and need to be used early. Multiple contemporary imaging techniques, including TEE, cardiac magnetic resonance imaging, and computed tomography, have shown equivalent accuracy for diagnosis of AAD.[10-13] The speed, portability, and versatility of TEE has resulted in its becoming the preferred diagnostic modality for diagnosis of AAD in many centers. Transesophageal echocardiography can identify and localize aortic dissection and furthermore identify most complications such as aortic insufficiency, pericardial effusion, periaortic hematoma, and branch vessel compromise. Previous work from IRAD has identified a number of demographic and clinical variables associated with a worsened prognosis in AAD[3,7,8,19,20]; however, the independent predictive impact of TEE findings has not previously been reported.

Prognostic role of TEE

The results of our study have confirmed that AAD carries substantial inhospital mortality and morbidity, even in centers with extensive expertise in treating this disease. Left untreated, mortality in acute type A dissection has been reported to be as high as 75% to 90% at 30 days. The IRAD experience suggests a somewhat lower medical mortality and was 50% in the series reported here. As with our previous reports involving

Table V. Prediction models with clinical and TEE variables for type A medical patients

Model variables	Overall medical type A %	% Among survivors	% Among deaths	Parameter coefficient	P	Death, OR (95% CI)
Model 1: clinical variables (c-index 0.79)						
Age ≥70 y	56.8	54.5	59.1	0.14	.79	1.15 (0.40-3.30)
Male sex	47.7	43.2	52.3	−0.83	.13	0.43 (0.15-1.26)
Sign coma/altered consciousness	21.2	7.1	34.9	2.21	.003	9.07 (2.12-38.75)
Presenting hypotension/shock	26.5	12.2	40.5	1.92	.003	6.84 (1.89-24.68)
Model 2: general clinical variables on presentation (c-index 0.86)						
Age ≥70 y	56.8	54.5	59.1	−0.74	.43	0.48 (0.078-2.94)
Male sex	47.7	43.2	52.3	0.16	.86	1.18 (0.19-7.37)
Presenting hypotension/shock	26.5	12.2	40.5	1.86	.08	6.39 (0.82-49.98)
Sign coma/altered consciousness	21.2	7.1	34.9	2.84	.008	17.08 (2.09-139.48)
TEE variables						
Patent false lumen	46.9	25.8	66.7	2.37	.007	10.65 (1.92-58.08)

the full IRAD cohort (independent of imaging modality), a number of clinical variables were highly associated with prognosis. Along with age, signs and/or symptoms of organ malperfusion and clinical instability (pulse deficits, renal failure, hypotension, and/or shock) increase the risk of death. Fluid extravasation into the pericardial or pleural space and/or mediastinum detected by TEE may be a sign of periaortic hemorrhage and impending rupture and has obvious clinical and prognostic implications.

Conversely, the presence of a dissection flap confined to ascending aorta and/or complete thrombosis of the false lumen seems to confer a more favorable prognosis. False lumen thrombosis results in the absence of flow and low pressure in the false lumen. Consequently, there is lower wall stress on the aortic wall and a reduced likelihood of further propagation of the dissection.[4,21]

The cause of death in AAD is multifactorial. One subset of patients died of cardiovascular complications such as acute severe aortic insufficiency, aortic rupture, cardiac tamponade, or compromise of the coronary circulation leading to myocardial infarction. Generally, these complications occur early in the course of AAD as the dissection is actively "propagating." Other causes of death are the result of major organ system failure and vascular compromise from propagation of the dissection into the renal, mesenteric, or other great vessels. In the presence either of AAD confined to the ascending aorta or thrombosis of the false lumen, propagation of the dissection to the distal vasculature with major organ compromise is less likely, thus reducing delayed morbidity and mortality.

There are several other findings noted on TEE that deserve comment. First, we observed that the site of origin of dissection did not impact prognosis once the ascending aorta was involved. The only aspect of the dissection flap correlating with patient outcome was dissection confined to the ascending aorta. Other echocardiographic features such as additional communication points or the presence of aortic regurgitation were not related to acute survival. However, it is not unlikely that additional factors such as size of entry and reentry sites, early false lumen dilation, and partial or complete thrombosis occurring after hospital discharge are related to long-term outcomes as well.

From the perspective of TEE, a relatively "low risk" ADD would be characterized by involvement limited to the ascending aorta with a thrombosed false lumen and no evidence of loss of integrity of the outer aortic wall such as pericardial effusion or adventitial hematoma. False lumen patency TEE heralded an adverse prognosis presumably by allowing additional propagation of dissection and hence further organ malperfusion syndromes or aortic expansion and rupture.

This study is unique in that it also evaluated the independent value of TEE and clinical findings in patients who underwent surgical therapy versus those who did not. When the medically treated subjects were excluded from the multivariable analysis, several TEE variables no longer predicted outcome. These included location of the dissection flap confined to the ascending aorta, false lumen patency, and evidence of pericardial effusion or tamponade. For the surgical subgroup, the only TEE variable associated with outcome was the presence of periaortic hematoma (OR 2.59, 1.06-6.32, $P = .04$).

The finding of a patent false lumen on TEE remained a strong prognostic indicator in medically treated patients (OR 10.65, 1.92-58.08, $P = .007$), whereas either complete or partial false lumen thrombosis was protective. The presence of false lumen thrombosis may suggest a "completed event" with less likelihood of further propagation of the dissection and compromise of

major organs. This medical survival is substantially greater than previously reported and suggests that there may be a subset of individuals in whom the AAD is relatively limited and in whom there is echocardiographic evidence of a stable aortic wall where further propagation is unlikely, and for whom survival may be substantially better than previously thought. A similar observation has been reported in chronic aortic dissection, where complete thrombosis of the false lumen, predominately in the descending aorta, was associated with improved outcome.[21] Although this study evaluated only TEE findings, it is reasonable to assume that similar findings on other imaging modalities may have similar implications.

Study limitations

The IRAD experience is the largest study of acute aortic dissection in recent years, reflecting the experience of high-volume referral sites across the world. It only comprises patients who were alive at the time of diagnosis and does not include patients who died before presentation to the hospital or before diagnosis. The IRAD includes only acute dissections, not chronic; and these data should not be extrapolated to the chronic dissection patient. It comprises data collected both prospectively and retrospectively from unselected and consecutive AAD patients with a wide range of clinical presentations and irrespective of treatment strategies. The TEE data are based on review of patients' medical records, not on actual blinded review of imaging data. In addition, it is unclear the degree to which findings on TEE may have resulted in early versus delayed surgery or in a decision to treat medically.

Conclusions

In addition to confirming the diagnosis and location of AAD, TEE provides prognostic information above and beyond that provided by the clinical risk variables. A subset of patients with AAD may be identified on the basis of TEE variables who have improved survival compared with historical controls of AAD.

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Congestive Heart Disease

Temporal trends in clinical characteristics, treatments, and outcomes for heart failure hospitalizations, 2002 to 2004: findings from Acute Decompensated Heart Failure National Registry (ADHERE)

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Background The purpose of this study was to assess temporal trends in clinical characteristics, treatments, quality indicators, and outcomes for heart failure (HF) hospitalizations.

Methods Characteristics, treatments, quality measures, and inhospital outcomes were measured over 12 consecutive quarters (January 2002 to December 2004) using data from 159 168 enrollments from 285 ADHERE hospitals.

Results Baseline characteristics were similar or showed only modest changes, and severity of illness by logistic regression was unchanged over all 12 quarters. Inhospital treatment changed significantly over time with inotrope use decreasing from 14.7% to 7.9% ($P < .0001$). Discharge instructions increased 133%; smoking counseling, 132%; left ventricular function measurement, 8%; and β-blocker use, 29% (all $P < .0001$). Clinical outcomes improved over time, including need for mechanical ventilation, which decreased 5.3% to 3.4% (relative risk 0.64, $P < .0001$); length of stay (mean), 6.3 to 5.5 days; and mortality, 4.5% to 3.2% (relative risk 0.71, $P < .0001$).

Conclusions Over a 3-year period, demographics and clinical characteristics were relatively similar, but significant changes in intravenous therapy, enhancements in conformity to quality-of-care measures, increased administration of evidence-based HF medications, and substantial improvements in inhospital morbidity and mortality were observed during hospitalization for HF. (Am Heart J 2007;153:1021-8.)

Heart failure (HF) presents an enormous and rapidly growing public health burden in the United States. It is estimated that more than 5 200 000 patients have HF, and approximately 550 000 new cases are diagnosed each year.[1] In 2004, HF as the primary diagnosis accounted for 1 099 000 hospital discharges and more than 6.5 million hospital days.[1-3] The estimated cost of HF is $33.2 billion, with costs of hospitalization representing the largest component.[1] Heart failure also results in substantial morbidity and mortality.[4,5] Improvements in inhospital and outpatient management of HF may be associated with decreased morbidity, mortality, and costs.[3]

To understand the potential impact of changes in the management of HF, time-dependent observations are required, but data regarding the temporal trends in clinical outcomes are relatively limited. Studies from community cohorts have suggested that survival of patients with chronic HF has increased.[6,7] On the other hand, a study that analyzed 3 957 520 Medicare beneficiaries 65 years or older, who were hospitalized with HF between 1992 and 1999, showed stable demographics but no substantial improvement in 30-day mortality over this entire study period, despite the introduction of effective treatments for HF.[8] Whether alterations in the incidence, treatment, and survival with HF have impacted the characteristics of more contemporary patients hospitalized with HF has not been studied. Additional therapies and processes of care have become available for the management of patients hospitalized with acute decompensated HF, but little is known regarding their potential influence on treatment patterns and outcomes. The purpose of the present analysis was

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Table I. Demographic and medical history over 12 quarters, 2002 to 2004

	Q1 (n = 8220)	Q12 (n = 9610)	Q1-Q12 (n = 159168)
Demographics			
Age (y)			
Mean (SD)	72.0 (14.2)	71.8 (14.2)	72.4 (14.1)
Sex, n (%)			
Male	3957 (48.1)	4843 (50.4)	77011 (48.4)
Race/ethnicity, n (%)			
White	5708 (72.0)	6811 (73.3)	114236 (74.4)
Black	1801 (22.7)	2050 (22.1)	32341 (21.1)
Medical history, n (%)			
Atrial fibrillation	2442 (29.7)	2956 (30.8)	49225 (30.9)
Coronary artery disease	4739 (57.7)	5725 (59.6)	91459 (57.5)
COPD/asthma	2328 (28.3)	3112 (32.4)	49989 (31.4)
History of HF	6253 (76.1)	7304 (76.0)	120348 (75.6)
Hypertension	5878 (71.5)	7484 (77.9)	117626 (73.9)
Renal insufficiency	2281 (27.7)	2952 (30.7)	47869 (30.1)

Table II. Initial symptoms and evaluation over 12 quarters, 2002 to 2004

	Q1 (n = 8220)	Q12 (n = 9610)	Q1-Q12 (n = 159168)
Symptoms, n (%)			
Peripheral edema	5486 (66.7)	6272 (65.3)	104635 (65.7)
Fatigue	2889 (35.1)	2973 (30.9)	49940 (31.4)
Rales	5724 (69.6)	6182 (64.3)	105814 (66.5)
Initial evaluation			
Congestion on first chest x-ray, n (%)	5575 (75.7)	6791 (75.4)	108398 (74.6)
Left ventricular function			
LVEF, mean (SD)	35.8 (16.7)	38.5 (17.5)	37.8 (17.3)
LVEF <40% or moderate/severe (%)	3664/6598 (55.5)	4149/8325 (49.8)	67445 (51.3)
SBP, mean (SD) (mm Hg)	144.5 (33.5)	144.5 (33.3)	143.9 (33.2)
DBP, mean (SD) (mm Hg)	77.3 (19.9)	77.9 (20.4)	77.7 (20.2)
Creatinine, mg/dL, Q1 (median) Q3	1.0 (1.3) 1.9	1.0 (1.4) 2.0	1.0 (1.3) 1.9
BUN, mg/dL, mean (SD)	32.4 (21.5)	31.9 (21.1)	32.0 (21.0)
Sodium, mean (SD) (mmol/L)	137.7 (4.8)	138.2 (4.6)	138.1 (4.7)
Hemoglobin, g/dL, mean (SD)	12.5 (2.5)	12.1 (2.1)	12.3 (2.4)

LVEF, Left ventricular ejection fraction; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure.

to examine recent temporal trends in demographics, clinical characteristics, treatments, quality-of-care indicators, and inhospital outcomes among HF hospitalization episodes entered in the ADHERE.

Methods

This analysis is based on all hospitalization episodes in the ADHERE registry that were discharged from January 1, 2002, through December 31, 2004: a total of 159168 from 285 hospitals. Details of the objectives, design, and methods in ADHERE have been previously described.[9] ADHERE hospitals, community, tertiary, and academic centers, are located throughout the United States and are demographically representative of the nation as a whole.[9,10] The registry collects information on demographic features, medical history, clinical characteristics, initial evaluations, therapeutic management, and inhospital outcomes. Data are collected from medical records by trained abstractors at each participating site and are recorded with the use of an electronic case report form. Importantly, registry participation did not require any alteration of treatment or hospital care, and entry of data into the registry were not contingent on the use of any particular therapeutic agent or treatment regimen. Participating hospitals received quarterly benchmarked data reports regarding characteristics, treatments, quality measures, and clinical outcomes (a national benchmark report can be located at www.adhereregistry.com).[9] To ensure confidentiality, no unique patient identifiers were collected. Registry entries thus reflect individual hospitalization episodes, not individual patients, and each unique hospitalization during the study period is entered into the registry as a separate record. Each site's institutional review board approved the study protocol.

For this analysis, patient hospitalization episodes were grouped by successive calendar quarters. Demographic infor-

Table III. Medication use and JCAHO measures over 12 quarters, 2002 to 2004

	Q1	Q12	P
Oral medications before hospitalization in patients with LVSD* and history of HF, n (%)			
ACEI/ARB	1737 (66.5)	1739 (62.0)	.0007
β-blockers	1421 (51.3)	2206 (68.8)	<.0001
Aldosterone receptor antagonists	433 (16.8)	502 (20.7)	.0004
Diuretics	2487 (82.0)	2743 (80.7)	.19
Digoxin	1332 (43.9)	1165 (34.3)	<.0001
IV medications during hospitalization, n (%)			
Inotrope	1208 (14.7)	763 (7.9)	<.0001
Dobutamine	626 (7.6)	350 (3.6)	<.0001
Milrinone	340 (4.1)	151 (1.6)	<.0001
Dopamine	545 (6.6)	404 (4.2)	<.0001
Nitroglycerin	751 (9.1)	840 (8.7)	.36
Nesiritide	418 (5.1)	2054 (21.4)	<.0001
Diuretics	7237 (88.0)	8393 (87.3)	.16
Oral medications during hospitalization in patients with LVSD*, n (%)			
ACEI/ARB	2612 (81.8)	2794 (81.0)	.41
β-blockers	2130 (63.4)	3244 (82.6)	<.0001
Aldosterone receptor antagonists	916 (29.1)	1046 (34.6)	<.0001
Diuretics	2981 (81.4)	3303 (79.6)	.05
Digoxin	1942 (53.0)	1660 (40.0)	<.0001
Oral medications at discharge in patients with LVSD*, n (%)			
ACEI/ARB	2188 (83.8)	2521 (83.1)	.50
β-blockers	1987 (61.9)	3051 (80.1)	<.0001
Aldosterone receptor antagonists	836 (27.6)	974 (32.8)	<.0001
Diuretics	3107 (88.9)	3514 (87.2)	.02
Digoxin	1771 (50.7)	1540 (38.3)	<.0001
JCAHO measures, n (%)			
HF1: discharge Instructions	1502 (26.5)	4485 (61.7)	<.0001
HF2: LV function assessment	5628 (82.5)	7504 (88.9)	<.0001
HF3: prescription for ACEI	1990 (76.2)	2276 (75.0)	.31
HF4: smoking cessation advice	330 (29.9)	1128 (69.3)	<.0001

*Excluding contraindications for ACEI or β-blockers, as appropriate.

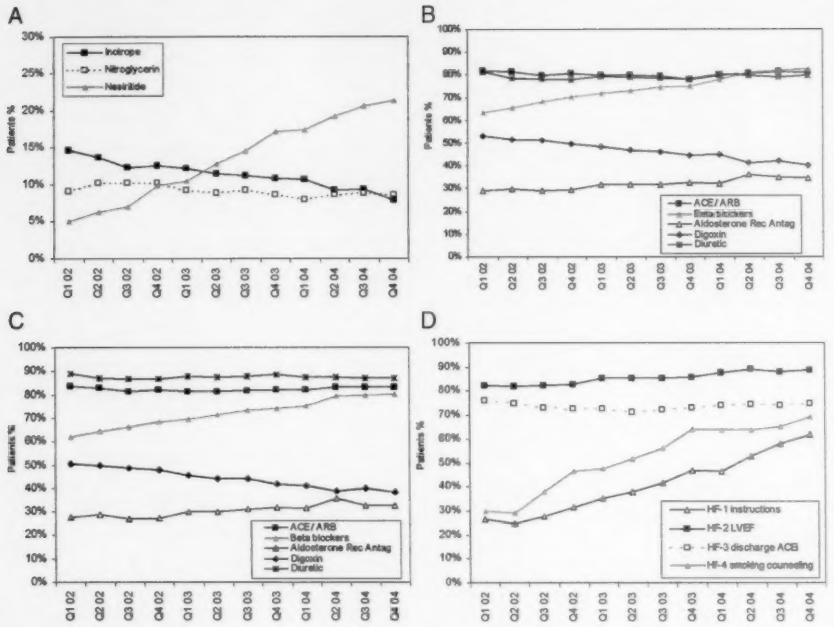
mation, medical history, baseline clinical characteristics, initial evaluations, laboratories, inhospital treatments, discharge therapies, and clinical outcomes were compared over time. Outpatient, inpatient, and discharge use of the following nonintravenous medications in patients overall and in those with documented left ventricular systolic dysfunction (LVSD) were examined: angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) (excluding patients with ACEI contraindication), β-blockers (excluding patients with contraindication), aldosterone receptor antagonists (excluding males with serum creatinine >2.5 mg/dL or females with serum creatinine >2.0 mg/dL at any time during hospitalization, and excluding patients with potassium >5.0 mEq/L), digoxin, and diuretics. The reported rates for outpatient medications before hospitalization are in those patients with prior history of HF, overall, and in those with documented LVSD. In addition, inhospital use of the following intravenous (IV) medications was assessed over time: all inotropes (dobutamine, milrinone, or dopamine), dobutamine, milrinone, dopamine, nitroglycerin, nesiritide, and diuretics. Left ventricular systolic dysfunction was defined as ejection fraction <40% or moderate/severe impairment. If inhospital ejection fraction assessment was not available, an assessment before the index hospitalization was used.

The 4 Joint Commission of Accreditation of Healthcare Organizations (JCAHO) core performance measures as defined during the study period were also assessed.[11] The inhospital morbidity and mortality clinical outcomes assessed over time were intensive care unit (ICU) admissions, need for mechanical ventilation during the hospital stay, inhospital mortality, ICU length of stay (LOS), and hospital LOS.

Statistical analysis

Descriptive statistics were used to characterize each of the study parameters: Means, SDs, medians, and interquartile ranges were used to summarize continuous variables, as appropriate, and percentages were used to summarize categorical variables. Trends in medication use, JCAHO core measure compliance, and outcomes over 12 quarters were assessed using the Cochran-Armitage trend test. Trends in LOS and ICU LOS were assessed using linear regression of log-transformed LOS on quarter of discharge coded as a continuous variable ranging from 1 to 12. Changes between Q12 and Q1 were examined using χ^2 test, 1-way analysis of variance, or Wilcoxon test, as appropriate. Two-sided P values were reported, and P values <.05 were considered statistically significant. A previously developed and validated inhospital mortality model was used to calculate expected mortality rates for each quarter based on patients' characteristics at presentation.[12] In addition, risk-adjusted mortality rates in each quarter were calculated using logistic regression. Of 80 demographic, medical history, and initial evaluation variables

Figure 1



Temporal tends over 12 quarters for (**A**) IV medications during hospitalization, (**B**) oral medications in patients with LVSD during hospitalization, (**C**) oral medication at time of hospital discharge, and (**D**) JCAHO core measures.

collected in ADHERE, classification and regression tree analysis and/or logistic regression models previously identified 8 variables (age, blood urea nitrogen [BUN], systolic blood pressure, diastolic blood pressure, creatinine, sodium, heart rate, and dyspnea at rest, as well as sex) as the most important risk factors for inhospital mortality.[12,13] Addition of up to 43 additional variables resulted in little incremental improvement in prognostic value.[12] In addition, year 2004 and 2003 were compared with year 2002 for variables exhibiting seasonal variation: inhospital mortality and hospital LOS. Records with missing data were excluded from analyses relevant to those data. For demographic and medical history parameters, less than 0.1% of data were missing. For initial evaluation, between 0.4% and 3.4% of records had missing data for blood pressure, heart rate, creatinine, sodium, BUN, or hemoglobin. Ejection fraction was not available in 27 746 (17.4%) of 159 168 hospitalizations. All analyses were carried out using version 8.2 of SAS software (SAS Institute, Inc, Cary, NC).

Results

There were 159 168 hospitalization episodes that were entered during the 12 quarters, with a mean ± SD of 13 264 ± 3025 hospitalizations entered per quarter (range 8220 to 17 878).

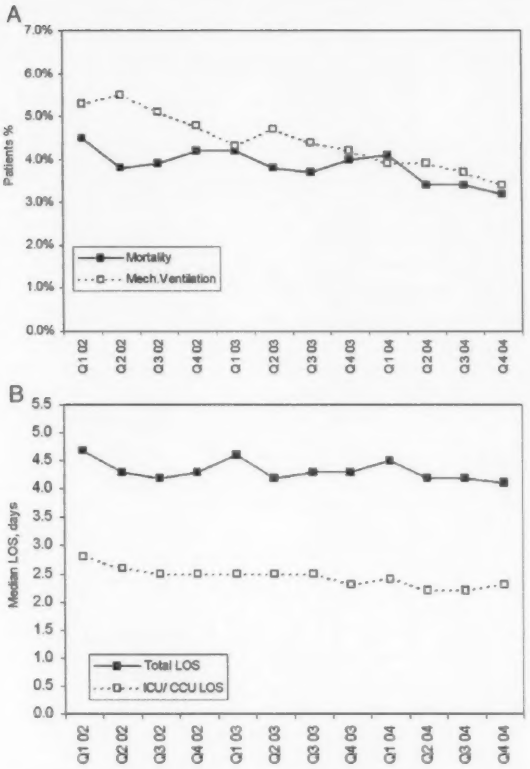
Characteristics

The mean age was 72.4 ± 14.1 years, 48.4% were male, and 74.4% were white. Overall characteristic, Q1, and Q12 are shown in Table I. From Q1 to Q12, there were small changes in demographic characteristics across the 12 quarters of observation. In ADHERE, 75.6% of hospitalization episodes had a previous history of HF, and this proportion did not change significantly over time. Comorbidities were frequently present. There were modest but statistically significant increases in the proportion with history of hypertension, chronic obstructive pulmonary disease (COPD), and chronic renal insufficiency from the 1st to the 12th quarter of observation (Table I). The proportion with peripheral edema, fatigue, pulmonary rales, or LVSD showed small decreases over time (Table II). There was no substantial change in admission BUN, sodium, blood pressure, or hemoglobin levels from Q1 to Q12 (Table II). These results indicate that the clinical presentation showed little to modest variation during the period of observation.

Treatment patterns

Temporal trends in HF treatment over the 12 quarters are shown in Table III and Figure 1. Over the 12 quarters,

Figure 2



Temporal trends over 12 quarters for (**A**) need for mechanical ventilation and inhospital mortality and (**B**) total hospital and ICU LOS.

significant changes occurred in the use of certain oral medications (Table III, Figure 1, *B* and *C*). Similar results were observed in the overall cohort and in patients with documented LVSD for oral medications; thus, only the results in the LVSD cohort are reported below. The use of β-blockers and aldosterone receptor antagonists rose substantially over time, whereas digoxin use fell before hospitalization, during hospitalization, and at discharge (all *P*[trend] < .0001). There were 34%, 30%, and 29% increases in the use of β-blockers before hospitalization, during hospitalization, and at discharge, respectively, from Q1 to Q12. No trend was detected in the use of ACEI/ARB over time (*P*[trend] = .27, .60, and .23 before, during, and at hospital discharge, respectively). The use of oral diuretics modestly decreased at admission without change at hospital discharge during the 12 quarters (*P*[trend] = .0003, .05, and .94 before, during, and at hospital discharge, respectively). Significant changes also occurred in the administration of IV HF medications (Figure 1, *A*; Table III). Inhospital use of inotropic agents fell almost 2-fold from Q1 to Q12 with the greatest percentage reduction in the use of milrinone (all *P*[trend] < .0001). Nitroglycerin use did not change during the 2002 to 2004 period, whereas nesiritide use rose substantially (*P*[trend] < .0001). Intravenous diuretic use remained high throughout the analysis period (≥87%), showing no significant change over time (*P*[trend] = .09).

Quality-of-care indicators

Significant improvements were found in compliance rates of 3 of 4 JCAHO HF quality-of-care indicators over the analysis period (Figure 1, *C*). Discharge instructions increased 133%; smoking counseling, 132%; and left ventricular (LV) function measurement, 8% (all *P* < .0001) (Table III) (all *P*[trend] < .0001). In contrast, prescriptions for ACEI at discharge among eligible patients did not change significantly over the study period (*P*[trend] = .30).

Inhospital outcomes

The expected inhospital mortality rate, based admission characteristics and the previously validated ADHERE risk model, did not change significantly over the study period (*P* = .99), ranging from 3.7% to 3.9%. In contrast, the actual unadjusted inhospital mortality rates observed decreased significantly over time from 4.5% to 3.2% (relative risk 0.71, *P*[trend] < .0001) (Figure 2, *A*; Table IV). The multivariable risk-adjusted mortality rate declined from 4.5% in Q1 to 3.1% in Q12 (odds ratio [OR] 0.75, 95% confidence interval [CI] 0.64-0.89, *P* = .0006). Adjustment for additional variables including history of hypertension, COPD, chronic renal insufficiency, fatigue and rales, and oral medications before hospitalization did not change the results substantially. During the 12 consecutive quarters, the need for mechanical ventilation decreased significantly from 5.3% to 3.4% (relative risk 0.64, *P*[trend] < .0001) (Figure 2, *A*; Table IV). The rate of ICU admissions fell by 20% (*P*[trend] < .0001). ICU LOS and hospital LOS decreased over time (both *P*[trend] < .0001) (Figure 2, *B*). Median ICU LOS decreased by half a day over the 12 quarters (Table IV).

Similar to previous reports in chronic HF,[14] inhospital mortality showed some seasonal variation with higher mortality rates observed in the first quarter of each year (Figure 2, *A*). On an annual basis, mortality rates of 4.1%, 3.9%, and 3.5% were observed in 2002, 2003, and 2004 discharges, respectively (OR for 2004 vs 2002, 0.86, 95% CI 0.81-0.92, *P* < .0001). Annual multivariable risk-adjusted mortality decreased from 4.0% in 2002 to 3.5% in 2004 (OR 0.87, 95% CI 0.81-0.93, *P* < .0001). On a yearly basis, median hospital LOS was 4.3, 4.3, and 4.2 days, and mean LOS was 5.9, 5.8, and 5.7 days for 2002, 2003, and 2004 discharges, respectively. Median LOS

Table IV. Inhospital outcomes over 12 quarters, 2002 to 2004

	Q1	Q12	P
Outcomes			
Inhospital mortality, n (%)	372 (4.5)	303 (3.2)	<.0001
Mechanical ventilation, n (%)	439 (5.3)	325 (3.4)	<.0001
ICU admissions, n (%)	1555 (18.9)	1460 (15.2)	<.0001
ICU/CCU, Q1 (median) Q3	1.4 (2.8) 5.0	1.3 (2.3) 4.1	.0002
Total LOS, Q1 (median) Q3	2.9 (4.7) 7.7	2.8 (4.1) 6.7	<.0001

CCU, Cardiac care unit.

was significantly lower in 2004 as compared with 2002 discharges ($P = .0004$).

Discussion

Results from this analysis indicated that in 159 168 HF discharges, there were only minor appreciable differences in the demographic characteristics or clinical status over the 3-year study period. During this period, there were significant changes in treatment patterns and quality-of-care indicators. Use of IV inotropes declined, whereas the use of vasodilator agents increased. The use of β-blockers increased substantially. The rate of hospital compliance with 2 JCAHO core performance measures (discharge instructions and smoking cessation advice) rose markedly. These improvements in treatment patterns and performance measures paralleled significant improvements in clinical outcomes, including declines in ICU admissions, need for mechanical ventilation during the course of hospitalization, LOS, and risk-adjusted inhospital mortality.

Prior studies have examined temporal trends in the quality of care for HF. Our findings both support and extend those findings. In 2 academic centers, the use of ACEI, β-blockers, and combination therapy increased from 1986 to 1993 and from 1990 to 1995 in outpatients with systolic HF.[15,16] Results from the Cardiovascular Health Study in elderly HF outpatients showed an increase in the use of ACEI from 1989 to 1990[17] and an increase in the use of β-blockers from 1989 to 2000.[18] However, the rate of change in β-blocker use over time was much smaller than in the current study. Another study examined 18 standardized indicators of quality-of-care in JCAHO-accredited hospitals and indicated steady improvement in the quality of care for myocardial infarction, HF, and pneumonia from the third quarter of 2002 through the second quarter of 2004.[19] Although we have gained valuable insights from prior studies of temporal trends in the quality of care for heart patients, few have addressed the 2002 to 2004 period, and only one has addressed use of IV therapy during hospitalization.

In contrast to a relatively stable demographic and clinical profile, this study showed significant changes in the administration of IV medications used to treat HF. There was a marked decline in the use of IV inotropes and a marked increase in the use of IV vasodilators. These changes in treatment patterns are important in view of evidence from clinical trials, indicating that the positive inotropic agent, milrinone, was not more efficacious than placebo for decreasing HF symptoms, morbidity, and mortality, but was associated with increased morbidity, mortality, and occurrence of adverse events.[20] Moreover, both small randomized clinical trials and observational analyses from ADHERE have suggested that, compared with IV vasodilators (nitroglyceride and nesiritide), the use of inotropic agents (dobutamine and milrinone) was associated with worsened outcomes.[13,21,22] Despite the scarcity of large-scale randomized clinical trials and lack of national guidelines regarding acute therapy during the study period, substantial changes in care occurred during this 3-year time frame. A recent analysis of 385 627 HF hospitalizations from 491 hospitals entered into the Premier database showed similar patterns of vasoactive medication use in the period that overlapped this study. From January to August 2001 compared with December 2004, nesiritide use at these hospitals increased from 0% to 15%, use of inotropic agents decreased from 15% to 9%, and use of nitroglycerine did not appreciably change.[23]

There were significant changes over the study period in the prescription of oral HF medications. β-blocker use before, during hospitalization, and at discharge increased substantially, whereas ACEI, ACEI/ARB, and diuretic use did not change appreciably. Change in the use of aldosterone receptor antagonists in potentially eligible patients increased but was less pronounced than that for β-blockers. From the first to the last quarter, clinically relevant changes in the rate at which hospitals conformed to the JCAHO core performance measures were also observed. Rates of assessing LV function were relatively high at the beginning of the analysis period and improved modestly over 3 years. In contrast, use of ACEI among eligible patients did not change appreciably over time. Even when ACEI/ARB use was analyzed, there was not appreciable change in use. Other studies have shown little change in ACEI/ARB use, and it remains unclear why, despite being a major focus of HF quality improvement efforts, the use of ACEI/ARB in eligible patients has not improved. These findings are particularly concerning because lack of use of ACEI/ARB is

associated with increased morbidity and mortality postdischarge among HF patients.[24,25] In contrast, β-blocker therapy use in eligible patients increased substantially during the study period because a multitude of clinical trials demonstrated benefits with this therapy.[3]

Determining which and to what extent any of these individual changes in management influenced clinical outcomes could not be adequately examined in this type of analysis and will require further study. Likewise, the extent to which prospective data collection, quarterly benchmarked reports, and other aspects of registry participation contributed to these observed improvements cannot be determined without comparison to control hospitals. During this study period, there were a number of national and regional efforts, such as JCAHO/CMS targeting improvement in discharge performance measures for patients hospitalized for HF, that may have contributed to some of these findings. However, none of the national initiatives focused on IV medications, β-blockers, or aldosterone antagonists in which the greatest changes in treatment were observed.

Although significant improvements have been made in the medical management of HF over time, it has been difficult to determine whether prognosis has improved for the typical hospitalized HF patient. The existing data are limited and their results inconclusive. One study of inhospital deaths showed a reduction in death rates from 1991 (6.9%) to 1995 (4.7%).[26] Similarly, a second study showed a decrease in death rates from 1985 to 1987 (8.4%) to 1994 to 1996 (6.1%).[27] A study of case fatality rates from 1986 to 1995 showed a 26% decrease in men and a 17% decrease in women,[28] whereas a second study of case fatality rates in the period from 1999 to 2000 showed no change from 1992 to 1999.[29] A study of 3 957 520 hospitalized Medicare patients between 1992 and 1999 showed no change in risk-adjusted 30-day mortality or 1-year mortality over this entire study period.[6] The current study demonstrates significant improvements in short-term clinical outcomes, including declines in ICU admissions, need for mechanical ventilation during the course of hospitalization, ICU LOS, total LOS, and inhospital mortality from 2002 to 2004.

It is important to note several limitations and strengths of this analysis. First, data for the ADHERE registry are observational in nature. As such, they preclude causal statements regarding the impact of changes in inhospital management and compliance with quality-of-care indicators on clinical outcomes. Second, these data are limited by the level of accuracy and completeness of initial documentation and of the abstracted data. The changes observed in treatment and outcomes in ADHERE hospitals may not be a representative of that in other hospitals, and we cannot exclude that some of the observed changes in treatment may have been influenced by virtue of the commercial sponsorship of ADHERE. ADHERE represents unique hospitalization episodes rather than unique patients, which may have influenced some of the findings. The risk prediction model was derived using ADHERE data from October 2001 to February 2003, overlapping with the first 4 quarters of this study population. Despite these limitations, this study has notable strengths. As a large, repository of real-time data from hospitals in all regions of the country, the ADHERE registry provides an opportunity to assess temporal changes in hospital outcomes in the context of concurrent changes in characteristics and approaches to care.

In conclusion, this study documented relatively stable demographic and clinical characteristics over 12 consecutive quarters from 2002 to 2004 among HF hospitalizations. In contrast, during this relatively short time frame, there were significant changes in IV therapy, enhancements in conformity to quality-of-care measures, and increased administration of certain evidence-based HF medications (eg, β-blockers). There were also substantial and clinically relevant improvements in clinical outcomes observed during the study period. These findings highlight the need for further efforts to accelerate improvements in the care of patients hospitalized with HF.

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β-Blocker dosing in community-based treatment of heart failure

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Background Community patients with heart failure (HF) are older, less often treated by HF specialists, and have more comorbidity than those in randomized clinical trials. These differences might affect β-blocker prescribing in HF.

Methods To explore patterns of β-blocker prescribing for HF in the community and their association with outcomes, we determined carvedilol doses at end titration in 4113 patients from a community-based β-blocker HF registry according to physician and patient characteristics, HF severity, and rates of hospitalization and death.

Results Female sex, age ≥65 years, and left ventricular ejection fraction ≥35% were associated with lower β-blocker doses. Average daily dose of β-blocker was lower with worse baseline New York Heart Association class. More patients of cardiologists achieved carvedilol doses ≥25 mg twice daily, whereas in those of noncardiologists lower doses were more common. Relative risk of HF hospitalizations or all-cause death was significantly lower with higher doses of β-blocker.

Conclusions β-Blocker dosing in community HF appears lower than in randomized clinical trials, especially when prescribed by noncardiologists. At all doses, patients taking the β-blocker carvedilol have a lower incidence of death and HF hospitalization than those discontinuing it, regardless of physician type in the community setting. (Am Heart J 2007;153: 1029-36.)

β-Blockers reduce morbidity and mortality when titrated to target doses in randomized clinical trials (RCTs) of patients with heart failure (HF). However, little is known about dosing of β-blockers in the community setting of HF or about the ability to achieve the same target doses in the community setting as were used in RCTs, where patients and physicians differ from those in the community.[1-4] Numerous reports have concluded that treatment of HF in community practice differs considerably from the protocols used in RCTs and from practice guidelines.[5-10] Treatment patterns in HF vary with physician type, practice setting, and patient populations and are typically characterized by widespread underutilization of recommended cardiac medications and by doses that are lower than those in RCTs.[6-10] Reasons for the lack of a standardized approach to HF management and achievement of less than recommended target doses are many and may include patient demographics, such as age and comorbidities, concern about adverse effects, and the prescribing philosophy of physicians in the community.[6-9]

Although large RCTs of β-blockers in HF have been inconsistent in demonstrating a clear dose-response relationship in respect to mortality and morbidity, they do indicate a survival advantage and reduction in HF-related hospitalizations when the dose of β-blockers is relatively close to the target dose.[11-18] In the community setting where patients often have more comorbidity and more use of concomitant medications, tolerability to higher doses, both perceived and real, may affect clinical outcomes. The purpose of this report was to explore the experience with prescribing a β-blocker, as observed in patients from the community-based COHERE, to relate the maintenance dose of carvedilol achieved to variables that could likely affect the dose achieved and might affect clinical outcomes.

Methods

Study design

The complete design and overall results of COHERE have been published elsewhere.[4,19] In brief, the COHERE observed

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experience with the β-blocker carvedilol in 4280 unselected community patients with HF. The only criterion for entry into the registry was that patients be adults starting carvedilol per the physician's usual practice for treating HF. Community-based physicians (cardiologists and noncardiologists) enrolled consecutive patients at their discretion and followed them during carvedilol dose titration and 1 year thereafter, managing them according to standard practice without a structured protocol. There were no required procedures or assessments other than to provide information about the patient's status and any clinical events at baseline, end titration (achievement of a maintenance dose of carvedilol), and at 6 and 12 months after end titration. To avoid influencing patient selection and usual practice of the participating physician, no background treatment was prespecified and training or advice on using carvedilol was not provided except to refer participant physicians to the package insert for carvedilol if they sought such advice.

A central institutional review board approved the registry plan, and all patients gave written informed consent. A scientific advisory council oversaw the design and conduct of the registry.[4,19]

For the present report, associations between the end titration (maintenance) dose of carvedilol and the following variables were analyzed: baseline clinical and demographic characteristics of patients; physician type described as cardiologist or noncardiologist; HF severity assessed by New York Heart Association (NYHA) classification; hospitalizations for HF; and deaths from any cause. Sufficient information for these analyses was available from 4113 (96%) of the total registry population. Patients were excluded if they were lost to follow-up before the required data became available. Patients who discontinued carvedilol before end titration continued to be followed up in the registry and were included in this analysis as the "0" dose group.

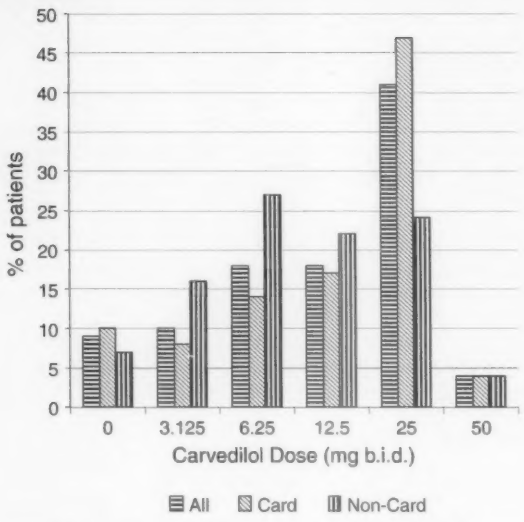
Statistical analyses

The detailed methods of statistical analysis have been described previously.[4,19] For the present analysis, patients were grouped according to carvedilol dose at the end of the dose titration period into the following groups: 0 (reference group), 3.125, 6.25, 12.5, 25, and 50 mg twice daily. Categorical data are presented as percentages of patients in each group. Significance testing between levels of categorical variables was performed using Pearson χ^2 or Fisher exact tests. Continuous variables are summarized and presented by sample size and mean ± SD. Significance testing was by analysis of variance and 2-sample *t* tests. The Cochran-Armitage trend test was used for significance testing for changes in NYHA class across dose groups to take into account potential linearity. McNemar test was used for comparing rate of hospitalizations for HF reported by the patient for the 12 months preceding registry enrollment to the rate observed during follow-up.

The mortality rate was determined as the Kaplan-Meier probability of death per 100 patient-years. Mortality hazard ratios using Cox proportional hazards models were calculated to compare dose groups, with adjustment for demographic and baseline characteristics known to be related to increased risk of mortality (ie, age and comorbidities), whether the participant had previously experienced a hospitalization, concomitant drug therapy, and physician type. Assumptions of proportional hazards were evaluated graphically and curves were determined to be parallel, thereby satisfying the statistical requirement. Morbidity rates were calculated as the percentage of patients in each dose group having a hospitalization for HF. Odds ratios comparing the 0 dose group, as the referent, to other dose groups were calculated using logistic regression. Hazard ratios and odds ratios were adjusted for patient demographics, comorbidities, vital signs, preenrollment hospitalizations, and concomitant drug therapy as well as for physician type in unstratified models.

All statistical analyses were conducted with Statistical Analysis Software, version 9.1.3 (SAS Institute, Cary, NC).

Figure 1



Carvedilol dose distribution at end titration by physician type. 0 mg dose indicates patients who had carvedilol discontinued by end of titration; $P < .001$ for distribution of patients treated by cardiologists versus patients treated by noncardiologists. *All*, All patients (N = 4113); *b.i.d.*, twice daily; *Card*, patients treated by cardiologists (n = 2994); *Non-Card*, patients treated by noncardiologists (n = 1119).

Results

Dose distribution

The dose distribution of carvedilol at end titration is summarized in Figure 1. The most common dose of carvedilol, achieved by 41% of the patients, was 25 mg twice daily. An additional 4% of patients in COHERE reached 50 mg twice daily, presumably based on body weight ≥85 kg, which was a weight-adjusted dose under consideration at the time. Notably, most of the patients (55%) were taking <25 mg twice daily at the end of titration, although only 9% had discontinued carvedilol (0 mg). Also shown in Figure 1 is a significant interaction

Table I. Dose distribution of COHERE patients by baseline characteristics

Patient characteristic	Carvedilol dose group (mg b.i.d.) 0 (n = 386)	3.125 (n = 416)	6.25 (n = 722)	12.5 (n = 759)	25 (n = 1672)	50 (n = 158)	*P* for distribution across dose range
Age (y)							<.001 (<65 vs ≥65 y)
<65 (n = 1646)	8	8	15	17	46	6	
≥65 (n = 2467)	10	12	19	20	37	2	
Sex							<.001 (male vs female)
Male (n = 2688)	9	9	17	18	42	5	
Female (n = 1424)	10	12	18	19	38	2	
Race							.086 (African American vs white)
African American (n = 493)	7	12	20	16	42	3	
White (n = 3315)	10	10	17	18	41	4	
History of							
Diabetes (n = 1301)	9	11	17	18	40	5	.023*
Hypertension (n = 2388)	9	11	18	18	40	4	.416*
MI (n = 1676)	11	10	17	19	40	3	.012*
LVEF (%)							<.001 (≤35% vs >35%)
≤35 (n = 2844)	9	9	15	18	44	4	
>35 (n = 1145)	10	12	22	19	34	3	
HF medications							
ACE-I (n = 3093)	9	9	16	18	44	4	<.001†
Digitalis (n = 2349)	9	10	16	18	42	4	.229†
Diuretic (n = 3145)	10	10	17	19	40	4	.183†
All 3 (n = 1579)	9	9	16	19	44	4	.010†

Values in rows represent percentages of patients in each dose group with the given characteristic. *b.i.d.*, Twice daily; *MI*, myocardial infarction.
*Compared with patients without the history.
†Compared with patients not taking the medication.

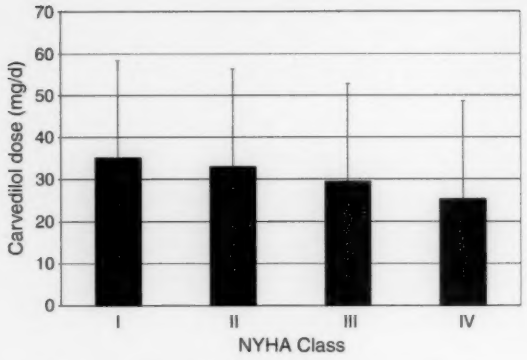
Table II. Dose titration: duration and vital signs

Patient group	Carvedilol dose group (mg b.i.d.) 0	3.125	6.25	12.5	25	50	*P*
Heart rate (beats/min)							
Baseline	77 ± 13	76 ± 13	78 ± 14	77 ± 14	78 ± 13	81 ± 14	<.001
Change	−2 ± 15	−2 ± 15	−5 ± 14	−7 ± 16	−8 ± 13	−10 ± 14	<.001
Systolic BP (mm Hg)							
Baseline	127 ± 21	127 ± 22	129 ± 21	129 ± 20	130 ± 20	131 ± 22	.2598
Change	−3 ± 19	−4 ± 20	−5 ± 20	−7 ± 20	−5 ± 19	−6 ± 21	.0036
Diastolic BP (mm Hg)							
Baseline	72 ± 12	73 ± 13	75 ± 12	74 ± 12	75 ± 12	78 ± 12	<.001
Change	−1 ± 11	−2 ± 12	−3 ± 12	−4 ± 12	−4 ± 12	−5 ± 13	<.001
Titration duration							
No. of days	62 ± 57	81 ± 90	87 ± 87	96 ± 77	90 ± 77	107 ± 106	<.001
No. of visits	2.8 ± 2.2	2.9 ± 2.2	3.2 ± 2.4	3.9 ± 2.1	4.5 ± 2.1	5.3 ± 2.1	<.001

Values are expressed as mean ± SD. *BP*, Blood pressure.

between physician type and β-blocker dose, as more patients of cardiologists achieved the 25-mg twice-daily regimen, whereas all the lower dose regimens were more commonly used by noncardiologists. The average twice-daily dose of carvedilol was significantly higher among patients of cardiologists compared with patients of noncardiologists (17 ± 12 vs 13 ± 11 mg, $P < .001$), but more patients of cardiologists also discontinued carvedilol during titration. The relationships between β-blocker dose achieved and baseline patient characteristics are shown in Table I. Significantly fewer women, patients ≥65 years old, and those with left ventricular ejection fraction (LVEF) >35% were titrated to the target doses of carvedilol of 25 to 50 mg twice daily and were more likely to be on lower doses than men, patients <65 years old, or those with LVEF ≤35%.

Figure 2



Carvedilol total daily dose by severity of symptoms.

Distribution of carvedilol doses was not related to race or history of hypertension, but was related to a history of diabetes, history of myocardial infarction, and to concomitant use of angiotensin-converting enzyme inhibitors (ACE-I), tending to be higher in patients with these characteristics.

Dose distribution by vital signs and duration of titration

The distribution of maintenance carvedilol doses according to heart rate, blood pressure, and duration of dose titration is summarized in Table II. Baseline heart rate and diastolic blood pressure were higher in groups receiving higher doses of carvedilol. At end titration, the largest changes in these variables were also observed in patients receiving the higher β-blocker doses. Not surprisingly, the duration of titration in terms of days or number of visits increased significantly as the dose of β-blocker achieved increased. It should be noted that the prescribing information for carvedilol at the time recommended titrating the dose every 2 weeks according to patient tolerability.

Dose distribution by severity of symptoms

As shown in Figure 2, the average total daily dose of carvedilol decreased as baseline NYHA class increased. Whereas this observation might suggest less tolerability to higher dose β-blockade in patients with more advanced NYHA class, no relationship to carvedilol dose was observed among the 9% of patients who discontinued it during titration (0 mg dose group), suggesting that inability to tolerate β-blockade was not simply related to severity of HF symptoms. At 1 year after completing carvedilol dose titration, NYHA class was unchanged in most patients, but the percentage who improved was highest and the percentage who worsened, lowest, in those receiving at least 12.5 mg twice daily.

Dose distribution and hospitalizations

The frequency of hospitalization for HF across dose groups is summarized in Figure 3. The percentage of patients hospitalized for HF during the follow-up period decreased significantly and progressively as the dose of β-blocker increased. Furthermore, comparing the groups taking some dose of β-blocker with the 0 dose referent group, we found the odds ratio for HF hospitalizations during follow-up fell significantly with increasing doses of carvedilol. These results were not affected by physician type. Compared with hospitalizations in the year before enrollment in COHERE, all groups, including 0 dose, experienced fewer HF hospitalizations during follow-up. Whereas the percentage reduction in hospitalizations compared to the previous year was significantly greater in all groups receiving the β-blocker (ranging from −48% to −71%, $P < .001$) compared with those no longer taking carvedilol (−26%), there was no significant relationship between the percent reduction in hospitalizations for HF and β-blocker dose.

Dose distribution and mortality

The percentage of patients dying from any cause was lower at each increment in prescribed carvedilol dose, as seen in Figure 4, and this effect was seen in the overall patient population as well as by physician type. The risk of death from any cause across dose groups is summarized in Table III. For the overall patient population, comparing the 0 dose group to dose groups taking the β-blocker, we found the hazard ratio decreased as β-blocker doses increased, with the decrease in risk of death achieving statistical significance at all doses >3.125 mg twice daily. This reduction in mortality risk at carvedilol doses >3.125 mg twice daily persisted when adjustments were made for age and NYHA class.

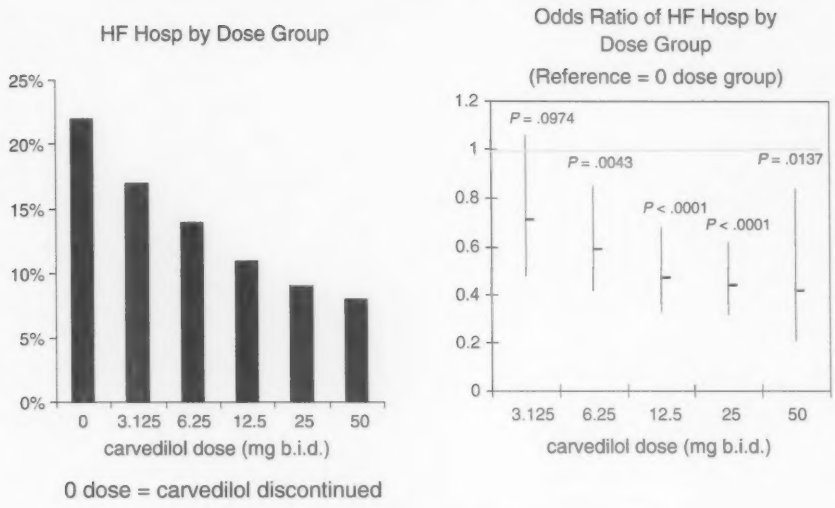
Discussion

In this community experience, prescribed doses of carvedilol were generally lower than those used in RCTs of HF in general where titration is closely monitored and may be forced upward, per protocol. Doses prescribed by noncardiologists were generally lower than those prescribed by cardiologists in COHERE; however, the average total daily dose of about 34 mg of carvedilol prescribed by cardiologists in COHERE is comparable with the experience of patients receiving carvedilol in COMET, where 75% of patients achieved 25 mg twice daily, taking an average total daily dose of 41.8 ± 14.6 mg.[20]

β-Blocker dosing for HF in the community setting

This registry experience of community-based physicians prescribing lower doses of β-blockers for HF is consistent with community experience in general and

Figure 3



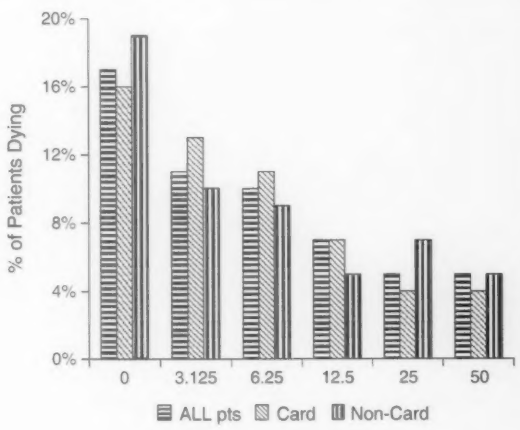
Carvedilol dose and hospitalizations for HF (HF Hosp).

with the ACE-I experience of primary care physicians in managing HF.[2,21,22] Despite the use of lower doses of carvedilol in COHERE, the observed incidence of hospitalization for HF and mortality experience, whether treated by cardiologists or noncardiologists, were in the same ranges observed in RCTs.[11,23] It must be emphasized, however, that any comparisons with RCTs are very tenuous, as patient and investigator populations involved in RCTs are usually quite different from those in a registry. It is noteworthy that in this registry, in general, patients who took any dose of the β-blocker had fewer adverse outcomes than those who discontinued the drug during titration. This is consistent with other RCTs in HF showing that lower doses of ACE-I or β-blockers are still beneficial.[17,24]

Baseline characteristics of patients and β-blocker dosing

Because this registry was specifically designed to observe community physicians' clinical practices while minimizing any influence on their usual practices, especially regarding the management of carvedilol dosing, we cannot completely address the reasons for physicians' decisions regarding use of carvedilol, but can only speculate about them. This likely explains why more than a quarter of patients enrolled had relatively preserved LVEF, that is, greater than the 35% upper limit used in carvedilol RCTs.[11] The lower doses of β-blocker used in this registry may relate to differences in characteristics between patients and physicians in the

Figure 4



Carvedilol dose and mortality.

registry compared with those in RCTs. In general, our patients were older, more likely to have preserved left ventricular systolic function, and included more women, diabetic patients, and hypertensives, with fewer of them taking ACE-I when compared with patients in the carvedilol RCTs.[11] Similarly, within this registry, patients treated by noncardiologists also were older with higher LVEF and included more women, diabetic patients, and

Table III. Carvedilol dose and mortality risk

		Carvedilol dose at end titration (mg b.i.d.)				
Patient group	**0**	**3.125**	**6.25**	**12.5**	**25**	**50**
All patients						
Hazard ratio (95% CI)	Ref	0.66 (0.42-1.05)	0.55 (0.36-0.84)	0.35 (0.22-0.54)	0.25 (0.17-0.39)	0.38 (0.16-0.93)
P		.078	.006	<.0001	<.0001	.034
Patients treated by cardiologists						
Hazard ratio (95% CI)	Ref	0.67 (0.39-1.17)	0.61 (0.37-1.00)	0.36 (0.22-0.61)	0.25 (0.16-0.41)	0.39 (0.13-1.15)
P		.1573	.0489	.0001	<.0001	.0894
Patients treated by noncardiologists						
Hazard ratio (95% CI)	Ref	0.74 (0.30-1.83)	0.50 (0.21-1.19)	0.30 (0.11-0.80)	0.28 (0.11-0.73)	0.35 (0.07-1.81)
P		.5203	.1175	.0170	.0093	.2107

Hazard ratios adjusted for patient demographics, comorbidities, vital signs, preenrollment hospitalizations, and concomitant drug therapy, as well as physician type (for all patients). *Ref*, Reference group.

hypertensives, with fewer of them taking ACE-I when compared with patients treated by cardiologists. In general, maintenance doses for β-blockade were lower in these subgroups, which may be significant, as some of these same subgroups are often underrepresented in RCTs of HF.

We observed higher baseline resting heart rates and greater reductions in heart rate in patients receiving higher β-blocker doses, which might suggest that physicians adjusted the dose to achieve a target heart rate. On the other hand, we observed similar relationships among baseline blood pressure, blood pressure changes, and carvedilol doses at end titration, and because blood pressures were, on average, in the reference range, it is unlikely that blood pressures were used to adjust doses. Furthermore, the heart rates achieved at end titration still averaged 70 to 73 beats/min, which is higher than target heart rates for titrating β-blockers used for other indications, that is, angina pectoris. Thus, it seems unlikely that the observed relationships between vital signs and β-blocker dosing were an important factor in dose titration. The observed longer duration of titration needed to achieve higher doses of carvedilol is consistent with the dose titration schedule recommended at the time. The observation that in the 0-dose group the average duration of titration was the shortest of all groups is also suggestive that in some patients side effects influenced the duration of dose titration.

Clinical outcomes and β-blocker dosing

The baseline characteristics associated with lower doses of beat-blockers are likely to also impact outcomes. For example, increased age, more severe NYHA class, and more concomitant illness would be expected to increase the risk of adverse outcomes, whereas more preserved LVEF should reduce these risks. There were some notable observations regarding β-blocker dosing and clinical outcomes. Patients receiving the higher maintenance doses of carvedilol had less severe baseline HF symptoms, as assessed by NYHA class, and more patients taking higher maintenance doses improved, whereas fewer worsened their NYHA class. Likewise, hospitalizations for HF and mortality rates during follow-up were also observed to be lower in patients taking higher maintenance doses of the β-blocker. It is unclear to what extent the observed associations between β-blocker dose and outcomes are a function of disease severity, as patients taking lower doses had worse baseline NYHA class but higher LVEF. We have not addressed in detail here the relationship among carvedilol doses, LVEF, and outcomes, which is the subject of another subgroup analysis from this registry published elsewhere.[25] Despite differences in characteristics of patients treated by cardiologists or noncardiologists, the same associations between β-blocker dose and clinical outcomes were observed in patients managed by either physician type.

Registry limitations

Conclusions regarding the impact of carvedilol dose on our observations are limited by the lack of controls in this registry approach. Our reference group in particular cannot be considered a true control group as it was composed of patients who were initiated on carvedilol but could not remain on it for whatever reason. As pointed out above, they were not different from the other groups in terms of NYHA class or LVEF at baseline and hence may not have been at greater risk of adverse outcomes as determined by these variables. Furthermore, their experience suggests that a small percentage of patients with HF in the community setting may not be able to tolerate β-blockade, for whatever reason, and that these patients appear to do worse than those who can tolerate some maintenance dose of a β-blocker. Thus, the characteristics of our patients and their physicians, as well as the observed outcomes, appear consistent with previous reports of HF experience in the community setting.[1-9,22] Therefore, it is reasonable to believe that the

present experience is representative of the community setting of HF. Additional potential study limitations are the lack of an a priori designed dose-response period or any prespecified dose-titration procedures. Because our goal was to observe usual practice without influencing it, we attempted to minimize data collection forms and procedures and may have failed to systematically record other significant information that might have influenced patient selection and carvedilol dosing, such as comorbidities like chronic pulmonary disease and renal insufficiency. Nevertheless, the present findings are consistent with reports of analyses of dosing in the community setting of HF and with those found in secondary analyses from RCTs.[8-10,17,18]

Conclusions

In summary, in the community setting, prescribed dosing of the β-blocker carvedilol for HF appears lower than in RCTs. The dose of β-blocker used in the community is associated with differences in NYHA functional class, patient demographics, and LVEF and tends to be higher when prescribed by cardiologists. At all doses, patients taking some β-blocker in actual practice appear to have a lower risk of death and hospitalizations for HF than those not receiving the drug. Based on these findings, the COHERE experience is consistent with the benefits of β-blocker therapy in RCT populations and indicates that lower doses of β-blockers may provide similar benefits in the community setting. This registry experience cannot address the relative benefits of the lower doses of β-blockers used in the community setting, which can only be adequately addressed by RCTs comparing lower and higher doses in that setting. Until results of such a trial are available, our findings are consistent with the recommendation that patients with HF treated in the community with β-adrenergic blocking drugs should be titrated, as tolerated, to the same target doses used in RCTs of these agents in HF.

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A meta-analysis of trials of pulmonary hypertension: A clinical condition looking for drugs and research methodology

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Background Various innovative pharmacologic strategies for the treatment of patients with pulmonary hypertension have been tested in recent years. Neither their comparative efficacy on surrogate end points nor the overall impact on mortality have been formally reviewed.

Methods We did a systematic overview of all randomized trials on the therapeutic yield of prostacyclin and analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors in patients with pulmonary hypertension searched in EMBASE, MEDLINE, and CINAHL databases from January 1985 to December 2005.

Results Sixteen trials involving 1962 patients met the inclusion criteria. Up to 80% of the patients were in functional class III/IV with a median walking distance of 330 m at baseline. Overall, experimental treatments were associated with (1) a nonsignificant reduction in all-cause mortality (relative risk 0.70, 95% CI 0.41-1.22), (2) a minor but statistically significant improvement in exercise capacity of 42.8 m (95% CI 27.8-57.8), and (3) an improved dyspnea status by at least one functional class (relative risk 1.83, 95% CI 1.26-2.66). Changes in exercise capacity were not found to be predictive of a survival benefit.

Conclusions Although confirming the limited benefits in clinical end points documented by each trial, the overview fails to support a significant survival advantage and does not support the predictive power of surrogate end points. (Am Heart J 2007;153:1037-47.)

Pulmonary hypertension (PH) is a devastating disease characterized by a sustained elevation of mean pulmonary artery pressure to >25 mm Hg at rest or >30 mm Hg with exercise and with a mean wedge pressure <15 mm Hg.[1,2]

The disease leads to progressive hypoxemia, right ventricular failure, and death, occurring from a few months to several years after diagnosis. An epidemiological survey conducted in the mid-80s on patients with primary PH revealed that half of the patients died within 2.8 years from the time of diagnosis, strongly depending on functional class.[3] The median survival of patients with New York Heart Association (NYHA) functional classes I to II was 6 years, 2.5 years for NYHA III, and only 6 months for NYHA IV patients. Other surveys of that period showed similar results.[4-6] These observations are assumed as the "natural history" of the disease without treatment with "modern" pharmacologic strategies.

Although the pathogenesis of primary PH is unknown, there is consensus that after an endothelial dysfunction/injury, a strong imbalance between antithrombotic/prothrombotic, vasodilatation/vasoconstriction, and growth inhibition/promitogen forces develops.[7,8] Three major pathways are recognized to play a role in this imbalance: the prostacyclin, nitric oxide, and endothelin pathways, which involve several mediators.[8]

Low levels of prostacyclin and an imbalance toward excess of thromboxane A_2 have been demonstrated in patients with PH.[9-11] Similarly, plasma levels of endothelin 1 are increased in patients with PH.[12-17] Finally, nitric oxide is a potent derived endogenous endothelium vasodilator that directly relaxes vascular smooth muscle cells. Decreased levels of nitric oxide synthesis have been reported in patients with PH.[18,19] Each of these pathways has been targeted with 3 different drug categories, namely, epoprostenol or other prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. These agents has been tested against placebo or control, providing a consistent evidence of benefit on the clinical end points of functional capacity,

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Table I. Baseline characteristics of trials

	Acronym	N	Active Intervention	Placebo	FUP	Etiology of PH (%)	NYHA III (%)	NYHA IV (%)
Rubin et al[25]	CIPPPH	23	E	No	2 m	IPAH (100)	65	26
Barst et al[26]	PPHSG	81	E	No	12 w	IPAH (100)	74	26
Badesch et al[27]	PHSSDSG	111	E	No	12 w	APAH (100)	78	17
Olschewski et al[28]	AIR	203	I	Yes	12 w	IPAH (50) APAH (22) TED (28)	59	41
Galiè et al[29]	ALPHABET	130	B	Yes	12 w	IPAH (48) APAH (52)	51	0
Simmoneau et al[30]	TSG	470	T	Yes	12 w	IPAH (58) APAH (42)	81	7
Barst et al[31]	BSG	116	B	Yes	9 m	IPAH (74) APAH (26)	47	0
Channick et al[32]	BPH	32	Bo	Yes	12 w	IPAH (84) APAH (16)	100	0
Rubin et al[33]	BREATHE-1	213	Bo 125 Bo 250	Yes	16 w	IPAH (70) APAH (30)	92	8
Barst et al[34]	STRIDE-1	178	SX 100 SX 300	Yes	12 w	IPAH (53) APAH (47)	66	1
Humbert et al[35]	BREATHE-2	33	E + Bo E	Yes	16 w	IPAH (82) APAH (18)	76	24
Ghofrani et al[36]	S&ISPH	30	S 12.5 S 50 S 12.5 + I S 50 + I	No	0	IPAH (33) APAH (20) TED (43) Other (3)	100	
Ghofrani et al[37]	SLFPH	16	S 50 E	No	0	APAH (25) Other (75)	62	38
Sastry et al[38]	SPPH	22	S	Yes	12 w	IPAH (100)	18	0
Galie et al[39]	SUPER-1	278	S 20 S 40 S 80	Yes	12 w	IPAH (63) APAH (30) Other (6)	58	3
Wilkins et al[40]	SERAPH	26	S 150 Bo 125	No	16 w	IPAH (88) APAH (12)	100	0

FUP, Follow-up; *ATT*, anti thrombotic therapy; *VD*, vasodilators; *DX*, digoxin; *DIU*, diuretics; *HD*, hemodynamic assessment; *E*, epoprostenol; *IPAH*, idiopathic pulmonary artery hypertension; *NR*, not reported; *APAH*, associated conditions PH; *I*, iloprost; *TED*, thromboembolic disease; *B*, beraprost; *T*, treprostinil; *Bo*, bosentan; *SX*, sitaxsentan; *S*, sildenafil.

albeit failing to support a survival advantage. This is possibly because of the very limited number of events over the short follow-up, which is the primary focus of this systematic overview. In addition, we aimed to investigate if the surrogate functional end points of efficacy are related to, or predictive of, a clinically relevant and effective benefit.

Methods

The commonly adopted approach of computer-aided literature search was applied to retrieve from EMBASE, MEDLINE, and CINAHL databases all randomized controlled trials published in English from January 1985 to January 2006 addressing the effects of prostacyclin, prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors in patients with PH. Randomized controlled trials involving patients with primary PH due to connective tissue disorders and PH related to thromboembolic disease were selected.

Sixteen trials have been included. Each study was used as a unit for statistical analysis. The data were analyzed by intention-to-treat. Main outcome measures for the present analysis were total mortality, NYHA class improvement, and exercise capacity assessed by the 6-minute walk test (EC6WT). Hemodynamic effects on pulmonary vascular resistance (PVR), cardiac index, and mean pulmonary artery pressure for individual studies are described but not used in the analysis because of missing values as well as difficulties in extracting data from published articles in a standardized way.

Statistical methods

Treatment effects for total mortality and NYHA improvement were evaluated as relative risks (RRs) according to the inverse-variance fixed-effect method.[20] When ≥ 1 trial had a null number of events in ≥ 1 group, a pseudocount method was used by adding a small constant equal to 0.25 and 0.50 to the number of events and the group size, respectively.[21] For exercise capacity, we computed the effect size of tested drugs by using the weighted mean difference, which was calculated after subtracting end-study exercise endurance (6-min walk distance) from baseline in treated and control groups. When studies did not directly supply the SE

Table I (continued)

ATT (%)	VD (%)	DX (%)	DIU (%)	Primary outcome measure	HD	Survival	Quality of life	Dyspnea assessment
100	43	17	56	EC6WT	Yes			
97	63	NR	NR	EC6WT	Yes	Yes	Yes	Yes
85	68	NR	NR	EC6WT	Yes	Yes	No	Yes
NR	54	NR	NR	NYHA/EC6WT	Yes	Yes	Yes	Yes
73	NR	19	53	EC6WT	Yes	Yes	No	Yes
NR	NR	NR	NR	EC6WT	Yes	Yes	Yes	Yes
NR	NR	NR	NR	Death/transplantation/rescue therapy/ >25% decreased P_{O_2}	Yes	-	Yes	Yes
72	47	NR	NR	EC6WT	Yes	No	No	Yes
71	47	NR	52	EC6WT	No	No	No	Yes
80	47	38	65	Change $P\bar{v}_{O_2}$	Yes	No	Yes	Yes
88	27	27	88	Total pulmonary resistance	Yes	No	No	Yes
NR	NR	NR	NR	Hemodynamic		No	No	No
NR	NR	NR	NR	Pulmonary vascular resistence index	Yes	No	No	No
NR	NR	NR	NR	Exercise time test	Yes	No	Yes	No
NR	NR	NR	NR	EC6WT	Yes	Yes	No	Yes
92	23	54	62	Right ventriclular mass	Yes	No	No	Yes

of the mean for the calculation of effect size, it was estimated from published data using the methods described by Greenland.[22] Alternatively, it was manually obtained from pictures described as follows: when either the value of the exercise capacity at the end of follow-up or the SE of the mean were not reported in the article, they were manually calculated from pictures (if available). We approached these multiarm studies combining all active arms in one and comparing it with the control group.

The Cochran Q test was used to assess the magnitude of effect size heterogeneity. When the heterogeneity test reached the formal level for statistical significance to assess heterogeneity ($P < .10$), the null hypothesis of homogeneity of the treatment effects across the studies was rejected and the analysis repeated by calculating a random-effect model.[23]

Sensitivity analyses were performed according to the pharmacologic category of tested drugs and disease severity (estimated using the median value of the 6-minute walk distance at baseline).

To examine the strength of the association between treatment effects on total mortality and the end-study change of exercise capacity, we fitted a univariate inverse variance-weighted linear regression with RR of total mortality as a dependent variable. The same weights that were obtained for the fixed-effect model were adopted for the regression analysis.

To assess the association between baseline exercise capacity and probability of death in the population of patients recruited in the various studies, we fitted both linear and polynomial linear regressions with death and baseline walking distance in the control group as dependent and explanatory variables, respectively. The regression models were weighted according to the dimension of the control group. Model comparisons were based on goodness of fit through the adjusted R^2.[24]

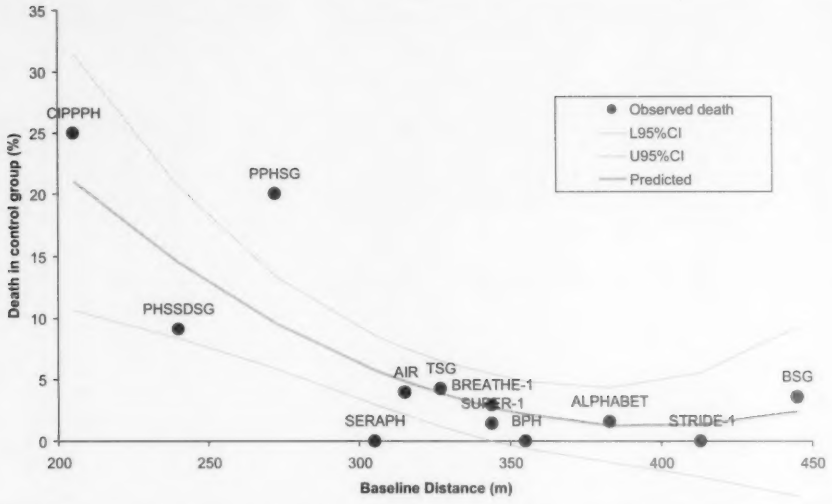
Results from all methods are reported along with their 95% CIs. All analyses were done using the SAS statistical package (SAS Institute, Inc, Cary, NC).

Results

Characteristics of studies

Table I presents a synoptic view of the 16 randomized clinical trials recruiting >1900 patients with PH[25-40] that have been published over a 15-year period (1990-2005). About 58%, 23%, and 19% of these patients were included in trials testing epoprostenol or other

Figure 1



Relationship between the mean walking distance at baseline and the rate of fatal events during the 3-month follow-up. Adjusted R^2 = 0.5519, P = .0109.

prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors, respectively. All trials but one were designed using control or placebo as comparator[40]; Humbert et al[35] assessed the efficacy of bosentan on top of epoprostenol therapy.

With the exception of Barst et al,[31] all studies had a short-term follow-up (mean 13 weeks).

Patients refractory to "conventional treatment" were included in the trials, although a broad variation in prescription patterns was observed between trials (eg, the use of vasodilators ranged from 23% to 68%).

The most frequently used efficacy end point was exercise capacity, assessed using the EC6WT.[25-27,29,30,32,33,39] Hemodynamic,[35-37] $P\bar{v}O_2$,[34] and right ventricular mass[40] changes have been used by 5 studies, whereas only 2 trials adopted composite measures of efficacy, including also fatal events. Seven trials assessed quality of life using a variety of instruments for this purpose.[26,28,30,31,34,38,40]

Clinical severity of the study populations

Nearly 65% of patients had a sporadic form of primary PH, whereas 30% had PH associated with other conditions (particularly collagen vascular disease). As to disease severity, the proportion of patients in NYHA/World Health Organization (WHO) dyspnea classes III and IV was around 70% and 11%, respectively.

The overall mortality of 3.2% (62 of the 1892 patients) was closely related to the baseline exercise capacity, accordingly, however, to the curvilinear relationship shown in Figure 1, which documents a progressively worsening prognosis of up to 20% for patients with low exercise capacity (<330 m) and an almost stable risk of death (about 5%) for patients with more preserved functional activity.

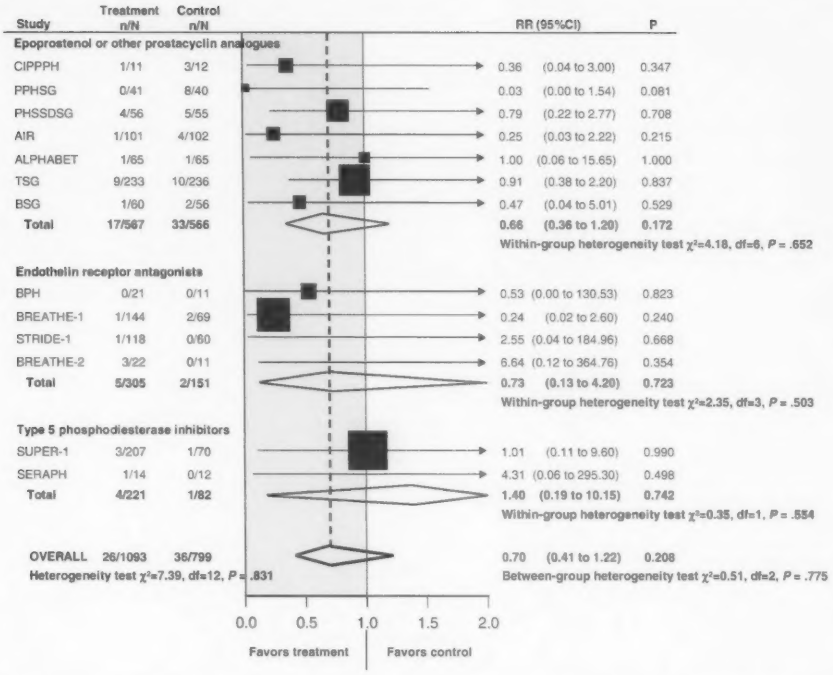
Effects of experimental treatments

Mortality. The cumulative RR estimate of death was a nonstatistically significant reduction of 30% (95% CI 0.41-1.22, P = .208) in the active treatment groups as compared with control groups (Figure 2), whereas no heterogeneity was apparent among studies (P = .831). With respect to the effects of prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors, no statistically significant between-group heterogeneity emerged in subgroup analyses in total mortality or between the subgroups testing each of the treatments.

As compared with studies recruiting patients with higher exercise capacity (≥330 m), those enrolling subjects with worse physical performance had definitely higher mortality rates (46/913, 5.0% vs 13/946, 1.4%). However, the proportional effect of tested treatments on mortality (RR) was 0.63 (95% CI 0.20-1.87, P = .43) versus severely impaired exercise capacity of 0.69 (95% CI 0.38-1.80, P = .25, between-group heterogeneity test P = .903) (Figure 3).

The absence of a relationship between baseline exercise capacity and/or its changes during follow-up and treatment benefits on mortality was confirmed by

Figure 2



Cumulative RR estimate of death in active treatment groups as compared with control groups (RR [95% CI]).

the results of the inverse variance–weighted linear regression with RR of total mortality as a dependent variable (Figure 4).

Exercise capacity. Experimental treatments significantly improved exercise capacity as assessed by the EC6WT. The weighted mean improvement of exercise capacity in patients allocated to experimental treatments was 42.8 m (95% CI 27.8-57.8, $P < .001$) (Figure 5), ranging from +10 to +93 m. The overall heterogeneity test provided statistically significant results; the between-group heterogeneity test, however, did not show heterogeneity of benefit between studies testing the 3 different drug categories ($P = .672$). Accordingly, the within-group heterogeneity test result for studies testing prostacyclin analogues was statistically significant ($P < .001$), thus indicating the existence of heterogeneous results in these studies, due to different recruitment criteria or play of chance.

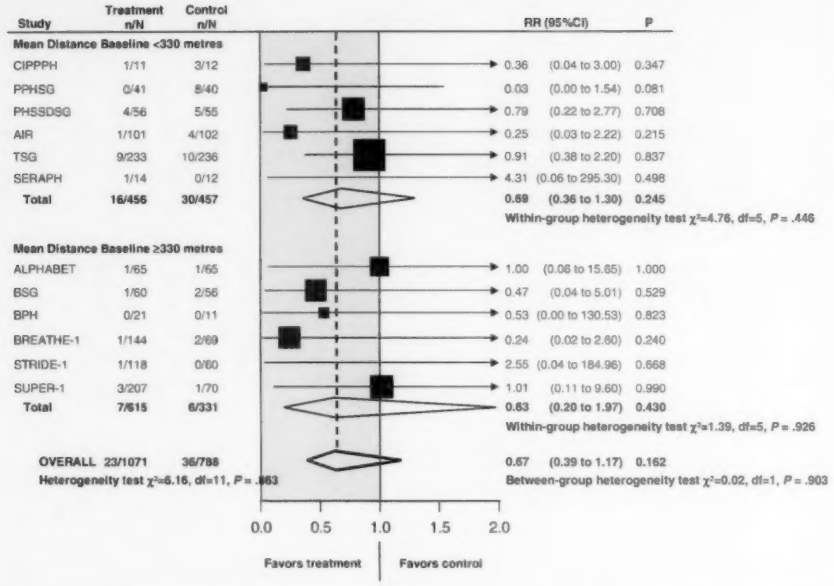
As compared with studies recruiting patients with less severe exercise capacity impairment at baseline, those including patients with more severe exercise capacity had a slightly higher, nonsignificant improvement in end-study exercise capacity (46.6 vs 38.6 m) (Figure 6).

Dyspnea status. As for trials reporting NYHA or WHO dyspnea status,[25-29,31-35] experimental treatments (RR [95% CI]) significantly improved dyspnea status by at least one functional class (RR 1.83, 95% CI 1.26-2.66, $P < .001$) (Figure 7). The pooled analysis showed that 33% (210/637) and 14.7% (69/469) of patients allocated to experimental and control treatments, respectively, had a significant symptomatic improvement. Statistical tests indicated the existence of heterogeneous study results that could not be attributed to drug categories (between-group heterogeneity test $P = .338$) and were concentrated in studies testing prostacyclin analogues.

Tested treatments were more effective in studies enrolling patients with more versus less pronounced impairment of exercise capacity at baseline (relative probability of improving functional class 4.64, 95% CI 1.52-1414, $P = .002$ vs 1.48, 95% CI 1.10-1.99, $P = .010$, between-group heterogeneity test $P = .043$) (Figure 8).

Other outcome measures. A relatively wide range of baseline values of PVR were observed at baseline in the various studies. The impact of treatments on PVR was usually statistically significant, the improvement in mean values ranging from 12% to 36% (Figure 9). Mean

Figure 3



Benefit of tested treatments on mortality related to baseline exercise capacity (≥330 m vs <330 m) (RR [95% CI]).

baseline pulmonary artery pressure varied approximately between 50 and 60 mm Hg.[25-37,39] Pharmacologic interventions determined in most cases a statistically significant reduction in end-study mean pressure, ranging from nearly 2% to 25%.

The tested treatments improved the cardiac index by 5% to 38%.

Discussion

Unambiguous major advances have been developed over the last years in the field of PH.[1,2,8] New insights into the molecular mechanisms and genetic background contributed to the design and further test of several pharmacologic agents[25-40] aimed at improving survival and quality of life of patients with PH. However, the cumulative benefits of these interventions on relevant clinical outcomes—particularly overall mortality—had not been reported.

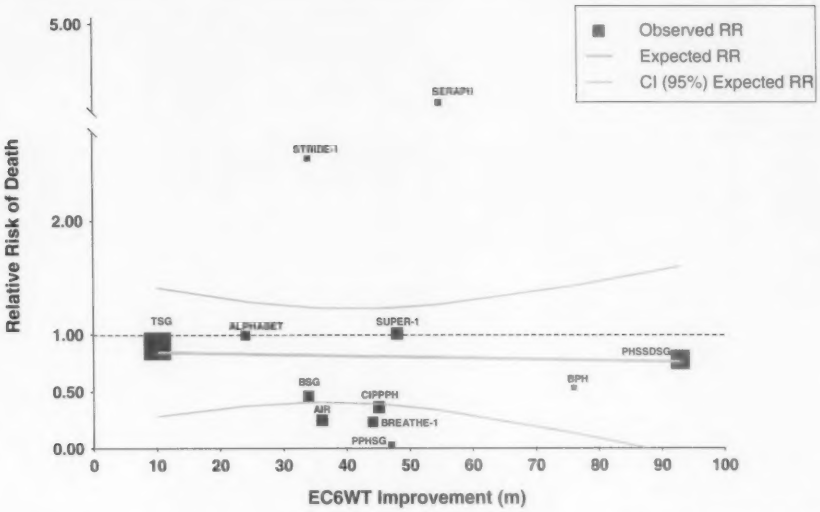
This meta-analysis provides 4 main results: (1) new agents were not associated with a statistically significant survival benefit among patients with PH; (2) No relationship was found between changes in exercise capacity and effect on survival; (3) treatments significantly improved dyspnea, exercise tolerance, and hemodynamic parameters; and (4) populations and methodology adopted in clinical trials were extremely homogeneous.

Clinical research was focused on severely ill patients with PH. Nearly 80% of patients included in the trials had NYHA/WHO dyspnea class III/IV, with half of the patients walking <330 m at the baseline 6-minute walk test. The main clinical priorities for this population were the demonstration of symptomatic improvement and were well tackled by clinical trials. In these populations, clinical trials[25-40] successfully demonstrated that all new treatments significantly improved exercise capacity and symptoms.

On the other hand, less symptomatic patients (NYHA/WHO class II-III and with a baseline exercise capacity >330 m) were less represented in the trials. In this population, median survival is 2.5 years for those in NYHA III and 6 years for those in NYHA II. For this reason, the main objective for this population should not be only exercise capacity and quality of life but overall survival and avoidance of clinical worsening as well as long-term safety concerns.

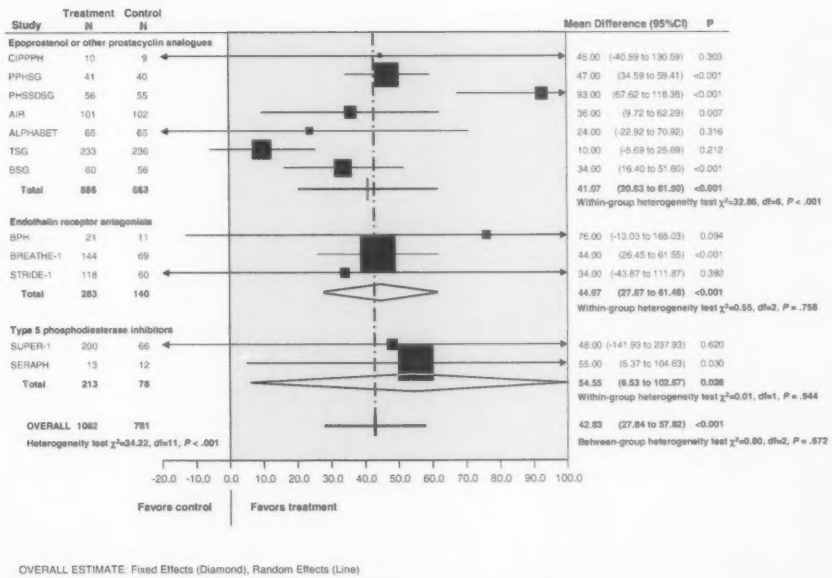
Despite clinical research being focused on a severely ill population, our analysis revealed a statistically nonsignificant 30% reduction in mortality in patients receiving experimental treatments and did not allow us to exclude a 22% increase in the risk of death. The cumulative number of fatal events documented in the trials could be expected to overcome the lack of power due to the combination of the small

Figure 4



Relationship between the degree of end-study improvement in exercise capacity and the degree of RR reduction of death (inverse variance–weighted linear regression).

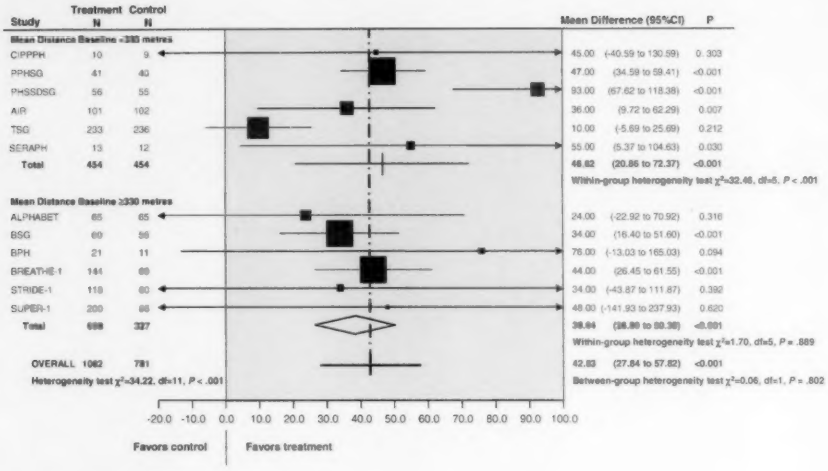
Figure 5



OVERALL ESTIMATE: Fixed Effects (Diamond), Random Effects (Line)

Weighted mean improvement of exercise capacity in patients allocated to experimental treatments as compared with control groups (RR [95% CI]). Note that the line of unity is not placed in the middle of the graph.

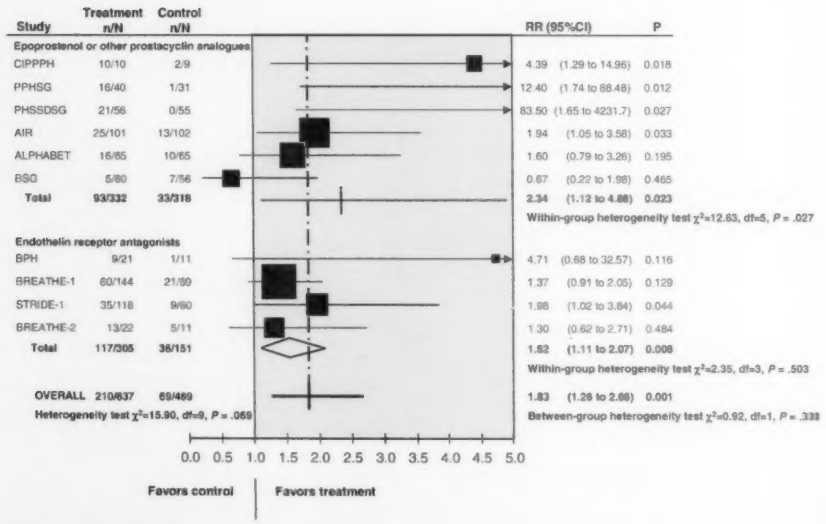
Figure 6



OVERALL ESTIMATE: Fixed Effects (Diamond), Random Effects (Line)

Improvement of exercise capacity related to baseline exercise capacity (≥330 m vs <330 m) (RR [95% CI]). Note that the line of unity is not placed in the middle of the graph.

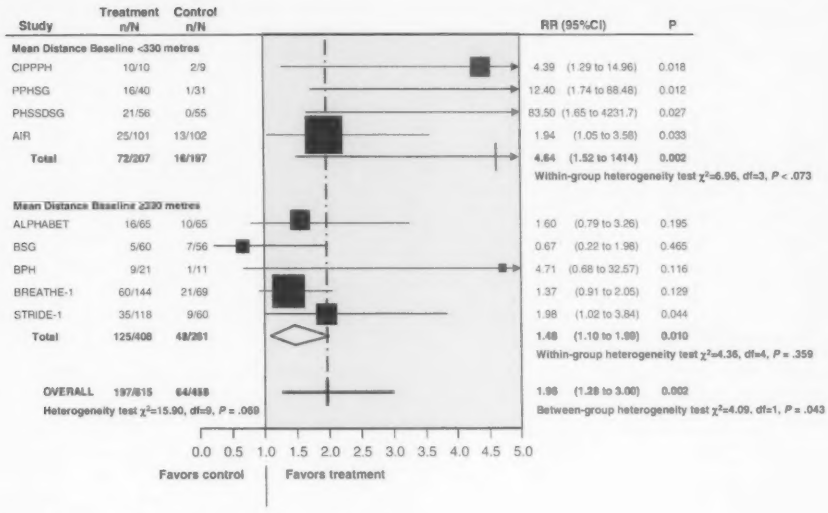
Figure 7



OVERALL ESTIMATE: Fixed Effects (Diamond), Random Effects (Line)

Improvement on dyspnea status (at least one functional class) in patients allocated to experimental treatments as compared with control groups (RR [95% CI]). Note that the line of unity is not placed in the middle of the graph.

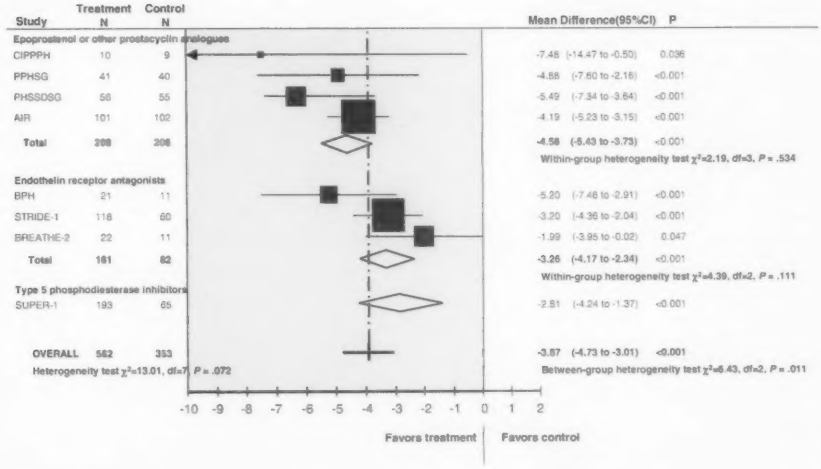
Figure 8



OVERALL ESTIMATE: Fixed Effects (Diamond), Random Effects (Line)

Improvement of dyspnea status related to baseline exercise capacity (≥330 m vs <330 m) (RR [95% CI]). Note that the line of unity is not placed in the middle of the graph.

Figure 9



OVERALL ESTIMATE: Fixed Effects (Diamond), Random Effects (Line)

Improvement in PVR in patients allocated to experimental treatments as compared with control groups (RR [95% CI]). Note that the line of unity is not placed in the middle of the graph.

samples sizes of individual trials and the short follow-up periods.

For severely ill patients, it is clear that a medication that improves function but does not prolong life might still be considered useful as long as it does not shorten survival. However, our findings should promote a reconsideration on the expectations that patients, physicians, and the health system currently have of these agents. To claim repeatedly that mortality reduction is already achieved and that it is not ethical to settle on mortality as an end point[41,42] is incoherent with both results and current agenda (in fact, all trials had been and are currently being designed to test experimental treatments against placebo/control).

Furthermore, although the statistically (though hardly clinically) significant benefit on exercise capacity shown in individual trials has been confirmed, no correlation has been found between this surrogate end point and mortality.

This negative finding is particularly worrying because one of the main reasons supporting the registration of the indication for each of the new and highly expensive (nearly $100 000 for parenteral prostacyclin, $80 000 for bosentan and inhaled iloprost, and from $12 000 to $50 000 for sildenafil per year, depending on the dose used) treatments was the predictive value of the surrogate measure on clinical outcomes.

Our analysis confirms that baseline exercise capacity is closely related to survival in patients with PH; however, this does not necessarily mean that changes in the distance walked could be used as a surrogate for mortality. This is not surprising, and medical literature offers several examples of mismatches between physiologic intuition and clinical outcomes. This is the case with ejection fraction and heart failure[43] or ventricular arrhythmias and arrhythmic death.[44] Despite baseline values predicting mortality, modification of these markers was not associated with clinical improvement (in fact, modifications worsened prognosis).

Results show that new treatments significantly improved exercise capacity with no heterogeneity in achieving this effect. In addition, prostacyclin and analogues as well as endothelin receptor antagonists improved symptoms.

This is important for the single severely symptomatic patient; however, it should be also underlined that the symptomatic improvement documented over such a short-term period can hardly be assumed as a completely satisfactory therapeutic tool to be used over a long-term period from a clinical, or—even less—from a public health perspective, particularly in view of the dearth of data on efficacy as well as safety over the long term.

New treatments moderately but significantly improve hemodynamic parameters. However, the clinical implications of these modification are less evident.

The meta-analysis has also allowed us to stress the substantial methodological weaknesses of the research strategies and designs that have characterized the latest generation of randomized controlled trials.

The truly surprising short-term follow-up appears hardly justifiable for testing therapies subsequently recommended with the support of surrogate end points, which, for the long term, are clearly unrelated with hard outcomes.

The recurrence over a 15-year period of the same unsatisfactory trial designs has led to the approval of a spectrum of drugs for which different mechanisms of action have been proposed, albeit producing nonheterogeneous results. No direct comparisons and no concomitant or sequential combinations of therapies have been provided.

It is noticeable that in the meantime, no reliable clinical epidemiological profiles have been published to allow at least indirect comparisons with the data and the expectations provided by previous studies.

The insufficient methodological quality of study designs (specifically with respect to sample size and/or duration of the follow-up) is often justified with the fact that PH is a rare disease.

The public health implications of registering drugs with an unclear evidence-based benefit profile (while imposing major economic burdens) require a substantial modification of approach.

The treatment of PH cannot be considered an evidence-based area; a more reliable assessment of already existing drugs could provide the basis for a more efficient testing of new molecules and/or of their sequences. A longer follow-up is the prerequisite for evaluating the relationship (if any) between surrogate and hard end points. Despite PH being a rare disease, the various groups currently working in the field—as well as all other groups with the same expertise—should make an additional effort to plan and conduct large, pragmatic, and clinically-oriented clinical trials.

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Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure

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Background Inflammatory markers are increased in chronic heart failure (CHF), including high-sensitivity C-reactive protein (hsCRP), but there is little information on its relationship to prognosis or other prognostic markers. We aimed to investigate the relationship between hsCRP and prognosis in patients with CHF and left ventricular systolic dysfunction (LVSD).

Methods Patients with CHF and LVSD (n = 957), but without infection or inflammatory disease, were identified. Patients had their medical history taken, underwent physical examination, had electrocardiographic and echocardiographic assessment, and had a 6-minute corridor walk test (6MWT) and blood tests, including hsCRP and N-terminal pro-B natriuretic peptide (NT-pro-BNP).

Results Patients with worse New York Heart Association class ($P = .02$), shorter 6-minute corridor walk test distance ($P < .001$), higher NT-pro-BNP levels ($P < .001$), anemia ($P < .001$), and renal dysfunction ($P < .001$), but not lower LV ejection fraction, had higher plasma concentrations of hsCRP. Patients with a CRP of >11.0 pg/mL had a hazard ratio for death of 3.0 compared with those with a CRP of <2.8 pg/mL ($P < .001$). Of 402 patients who had a second sample taken for hsCRP at 1 year, 46% showed a substantial change from baseline levels. Marked increases in hsCRP were associated with a fall in hemoglobin level. NT-pro-BNP was noted to be a more accurate prognostic marker than hsCRP (area under the curve of 0.74 compared with 0.67 for hsCRP, $P < .05$).

Conclusion Patients with CHF and LVSD have increased serum concentrations of hsCRP that are related to functional limitation and prognosis but not to the severity of LV ejection fraction. (Am Heart J 2007;153:1048-55.)

C-reactive protein (CRP) is an acute-phase protein. A component of the innate immune system, it protects the organism against microbial infection and limits the degree of tissue damage that the inflammatory process can cause.[1] It is produced in the liver in response to the cytokine interleukin 6 (IL-6).[2]

Heart failure is associated with the activation of cytokines, and increased plasma concentrations of some (eg, IL-6, tumor necrosis factor α [TNF-α], soluble tumor necrosis factor receptor 1, and soluble tumor necrosis factor receptor 2) are associated with a worse prognosis.[3] Such cytokine markers are not routinely available to clinicians caring for patients with heart failure, but the high-sensitivity assays for the acute-phase reactant, CRP, are widely available. Results from a study of 123 American patients with ischemic heart disease and left ventricular systolic dysfunction (LVSD) undergoing coronary angiography and a study of 188 Japanese patients with dilated cardiomyopathy suggested that those with an elevated high-sensitivity CRP (hsCRP) had a worse prognosis.[4,5] Of 214 patients presenting with acute heart failure, an elevated CRP was an independent predictor of death.[6] Recently, the Val-HeFT study reported that hsCRP was an independent predictor of morbidity and mortality in a large number of patients with heart failure enrolled in the trial.[7] Little is known however about the prognostic use of hsCRP in routine outpatient clinical practice.

We assessed the value of measuring hsCRP routinely in our outpatient clinic to address 4 questions. (1) Are mean serum concentrations of hsCRP increased in patients with chronic stable heart failure, consistent with an inflammatory response? (2) Is hsCRP level related to prognosis? (3) What is the relationship

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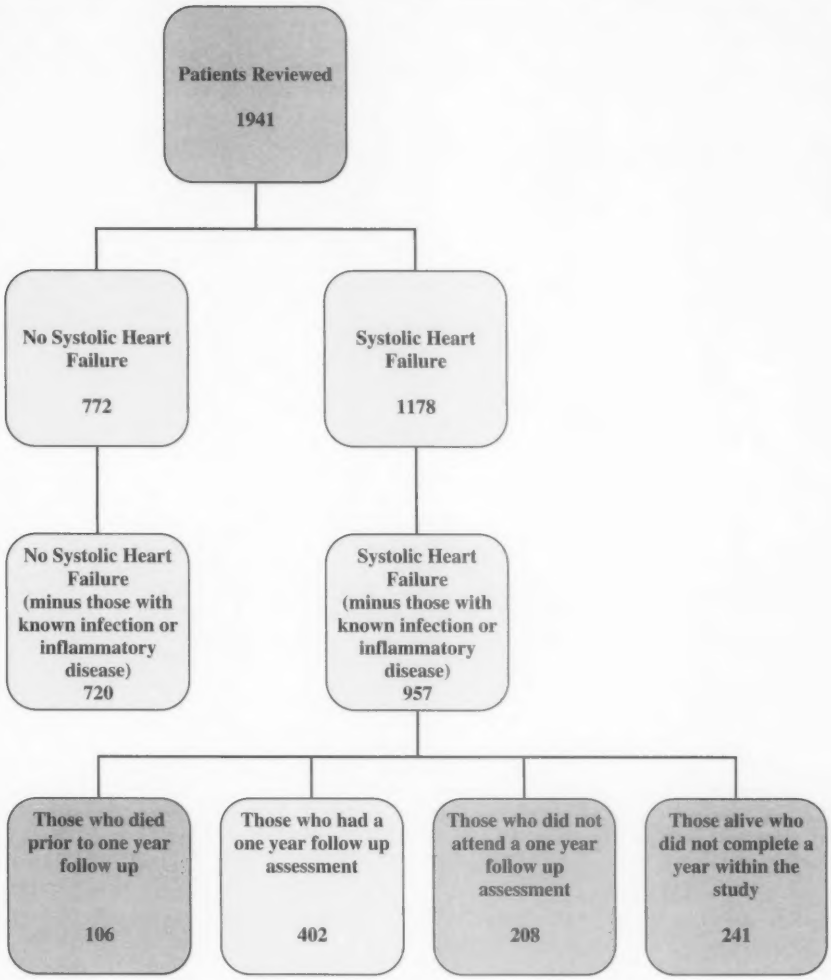
Figure 1



Trial profile.

between hsCRP and other commonly available prognostic markers? (4) Does a change in hsCRP over a 1-year period reflect a change in the patients' clinical status?

Methods

All patients referred to the heart failure clinic for the investigation of the presence and/or cause of heart failure had hsCRP routinely measured. Patients were referred directly to the clinic by physicians working in the community or from our hospital colleagues. All signed a standard informed consent form that was approved by our local ethics committee.

The principal population of interest was patients with a diagnosis of heart failure secondary to LVSD who were free of infection, other inflammatory diseases such as rheumatoid arthritis, or cancer that could cause elevation in hsCRP. We defined *infection* by clinical examination, current use of antibiotics, or a white blood cell count of $>12 \times 10^9$/mL. Those who had a hsCRP of >10 mg/L had their findings reviewed a second time and, if there was no obvious cause for their inflammation, they were included in the study.

Study design

Each patient had a baseline visit at which time they had a physical examination and medical history taken. The severity of symptoms was graded using the New York Heart Association

Table I. Baseline characteristics of the patient populations

	Those with LVSD	Those with LVSD (screened to remove those with a known inflammatory process)	Those with LVSD (screened to remove those with a known inflammatory process) reviewed at 1 y	Those without LVSD	Those without LVSD (screened to remove those with a known inflammatory process)
n	1178	957	402	772	720
Age (mean ± SD)	71 ± 10 y	71 ± 10 y	71 ± 10 y	71 ± 11 y	71 ± 11 y
Sex					
Male	835 (71%)	689 (72%)	289 (72%)	320 (41%)	300 (42%)
Female	343 (29%)	268 (28%)	113 (28%)	452 (59%)	420 (58%)
NYHA class					
I	187 (16%)	170 (18%)	72 (18%)	303 (39%)	299 (42%)
II	658 (56%)	506 (53%)	245 (61%)	349 (45%)	330 (46%)
III	307 (26%)	258 (27%)	80 (20%)	109 (14%)	86 (12%)
IV	26 (2%)	23 (2%)	4 (1%)	11 (1%)	5 (>1%)
LV impairment					
None	0 (0%)	0 (0%)	52 (13%)	772 (100%)	720 (100%)
Mild	359 (30%)	241 (25%)	125 (31%)	0 (0%)	0 (0%)
Moderate	476 (40%)	408 (43%)	169 (42%)	0 (0%)	0 (0%)
Severe	343 (29%)	308 (32%)	52 (13%)	0 (0%)	0 (0%)
Risk factors					
Current smoker	135 (11%)	123 (13%)	52 (13%)	108 (14%)	87 (12%)
Diabetes	230 (20%)	188 (20%)	76 (19%)	95 (12%)	89 (12%)
Hypertension	482 (41%)	385 (40%)	161 (40%)	390 (51%)	368 (51%)
Documented MI	483 (41%)	396 (41%)	165 (41%)	132 (74%)	125 (17%)
Diagnosis					
IHD	702 (60%)	655 (68%)	257 (60%)	182 (24%)	172 (24%)
DCM	309 (27%)	195 (21%)	88 (22%)	0 (0%)	0 (0%)
Hypertension	108 (9%)	73 (8%)	36 (9%)	210 (27%)	191 (27%)
Valvular	50 (4%)	27 (3%)	20 (5%)	40 (5%)	38 (5%)
Alcohol	2 (>1%)	2 (>1%)	0 (0%)	0 (0%)	0 (0%)
Arrhythmia	6 (>1%)	4 (>1%)	1 (>1%)	4 (>1%)	2 (>1%)
Congenital	1 (>1%)	1 (>1%)	0 (0%)	0 (0%)	0 (0%)
COPD	0 (0%)	0 (0%)	0 (0%)	259 (34%)	242 (24%)
Diastolic HF	0 (0%)	0 (0%)	0 (0%)	77 (10%)	75 (10%)
Medication					
Loop diuretic	842 (72%)	685 (72%)	310 (77%)	320 (41%)	285 (40%)
Thiazide	35 (3%)	30 (3%)	12 (3%)	53 (7%)	52 (7%)
ACEi	808 (69%)	669 (70%)	326 (81%)	265 (34%)	248 (34%)
ARB	73 (6%)	57 (6%)	44 (11%)	58 (8%)	57 (8%)
BB	598 (51%)	490 (51%)	338 (84%)	225 (29%)	217 (30%)
Statin	529 (45%)	441 (46%)	217 (54%)	233 (30%)	223 (31%)
Aldosterone antagonist	211 (18%)	184 (19%)	96 (24%)	41 (5%)	35 (5%)
Digoxin	196 (17%)	149 (16%)	68 (17%)	82 (10%)	76 (11%)
Aspirin	557 (47%)	453 (47%)	161 (40%)	286 (37%)	275 (38%)
Warfarin	261 (22%)	216 (23%)	117 (29%)	95 (12%)	87 (12%)
NSAID	33 (3%)	27 (3%)	8 (2%)	27 (3%)	25 (3%)
Allopurinol	61 (5%)	53 (6%)	28 (7%)	18 (2%)	16 (2%)
Amiodarone	91 (8%)	82 (9%)	32 (8%)	23 (3%)	20 (3%)
hsCRP (mg/L)					
mean (±SD)	12.9 (23.5)	10.9 (18.0)	7.7 (15.8)	7.9 (12.1)	7.3 (10.7)

MI, Myocardial infarction; *IHD*, ischemic heart disease; *DCM*, dilated cardiomyopathy; *COPD*, chronic obstructive pulmonary disease; *HF*, heart failure; *NSAID*, nonsteroidal anti-inflammatory drug.

(NYHA) class. Venous blood samples were taken for the measurement of hemoglobin, electrolytes, creatinine, N-terminal pro-B natriuretic peptide (NT-pro-BNP), and hsCRP. An electrocardiogram was performed followed by echocardiographic assessment of the heart. A standardized 6-minute corridor walk test (6MWT) was performed. All patients with a diagnosis of heart failure due to LVSD were followed up in the clinic. The diagnosis of heart failure was defined in accordance with the guidelines of the European Society of Cardiology.[8] Left ventricular function was determined from 2-dimensional echocardiography. Left ventricular ejection fraction (LVEF) was calculated using the Simpson's formula from measurements of end-diastolic and end-systolic volumes on apical 2-dimensional views, and LVSD was diagnosed if LVEF was ≤45%. In all of the echocardiograms, an eyeball assessment was made by the operator as to whether the LVSD was mild, moderate, or

severe. Diastolic impairment was diagnosed if LV systolic function was preserved, the left atrium was dilated, abnormal Doppler variables corrected for age, or atrial fibrillation was present, and the patient had current or previous evidence of fluid congestion (for instance radiologic pulmonary edema) or had substantial symptom relief with diuretics and no other likely cause of symptoms other than heart failure was present. N-terminal pro-B natriuretic peptide was not available to the clinician at the time of diagnosis.

Those patients diagnosed with LVSD were invited to attend a routine 1-year appointment. Those that agreed had the above investigations repeated. Patient mortality was ascertained when the study closed by searching the hospital clinical database.

C-reactive protein analysis

Samples for hsCRP were analyzed in the local laboratory. The majority, 1551 (80%), were measured using the Synchron LX 20 system CRPH reagent (Beckman Coulter, High Wycombe, UK) assay. The remaining 390 (20%) samples were measured using the Beckman Immage or Beckman Array assay. Samples were analyzed within 24 hours of being taken; those samples not analyzed within 2 hours were stored in a refrigerator at 2°C to 8°C.

The analytical range of the Synchron LX 20 system is 0.2 to 380 mg/L. Exclusion of samples measured using either of the older assays did not materially affect the results.

Statistical analysis

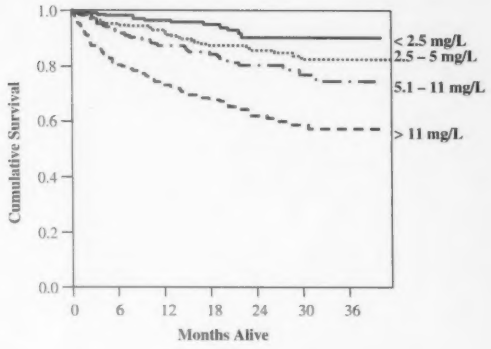
Data were analyzed using the SPSS/PC (version 11.5, SPSS Inc, Chicago, IL) software package. An arbitrary level of 5% statistical significance was assumed throughout (2-tailed). A linear least squares regression model was used to explore relationships between hsCRP and other potential prognostic markers. The results are presented as means both unadjusted and adjusted for age, sex, white blood cell count, presence of diabetes mellitus, smoking, β-blockers (BBs), statins, and nonsteroidal anti-inflammatory drugs. A Cox regression model was used to calculate hazard ratios with 95% CIs adjusting for the same variables as in the linear regression model. We used categorical rather than continuous data. This was to allow for simpler presentation and also to maximize the data so that we could include missing values and therefore get an estimate of bias from such groups. Kaplan-Meier curves are presented for the mortality data. The log-rank test was used to test the equality of survivor function across hsCRP groups. The relationship of hsCRP with BNP was examined using a receiver operating characteristic curve analysis.

Analysis of change in variables over a 1-year period

We wished to see if a change in the value of hsCRP from baseline to 1 year (ΔhsCRP) were associated with other prognostic variables in heart failure. To examine this we investigated changes over 1 year in hemoglobin, creatinine, and ejection fraction (as assessed by the Simpson's equation).

ΔhsCRP was classified into 5 groups based on the approximate quartiles of hsCRP found at baseline. If the hsCRP value changed by ±2.8 mg/L, we classified this as no change; if the hsCRP value changed between ±2.9 and 11 mg/L, we classified this as a minor increase or decrease; and if the value was ±11 mg/L, we classified them as having had a major increase or decrease.

Figure 2



hsCRP pg/ml	0 months	12 months	24 months	36 months
<2.5	251 (8)	163 (6)	62 (0)	8 (1)
2.5-5	238 (15)	177 (12)	105 (3)	22 (0)
5.1-11	249 (28)	160 (10)	82 (3)	18 (0)
>11	218 (55)	139 (10)	75 (4)	16 (0)

Kaplan-Meier curve of survival according to hsCRP values. In the table, values are expressed as the number of patients at risk (number of patients who died).

Results

Of 1941 patients referred to our clinic with a diagnosis of possible heart failure between September 11, 2001, and February 25, 2005, for whom hsCRP was available, the diagnosis of heart failure due to LVSD was made in 1178 patients. Heart failure was considered secondary to valve disease in 40 patients, but heart failure in the absence of LVSD or valve disease was diagnosed in only 77 patients, perhaps because the clinic policy discouraged such a diagnosis without definitive evidence of cardiac dysfunction. Many patients without LVSD had lung disease, obesity, or low levels of fitness creating uncertainty about the cause of their symptoms (Figure 1).

Of the 1178 patients with LVSD, 221 were excluded from the analysis because they had infection, another inflammatory disease, or cancer. The 957 patients with LVSD and no known inflammatory disease were followed up for 21 ± 10 months, of whom 106 died (11%) within 12 months. Of the 851 surviving to 1 year, 402 (47%) had a second complete assessment. Two hundred eight (22%) patients did not have a second sample taken either because of administrative error or because they defaulted from the visit.

Most patients were white (>99%), elderly (mean age, 71 ± 10 years), were in NYHA class I or II, and had ischemic heart disease; and 20% were diabetic (Table I).

Table II. High-sensitivity CRP and its relationship to other prognostic markers

Variable		n	HsCRP (median [IQR])	HsCRP (unadjusted mean)	HsCRP (adjusted mean [95% CI])	P
Hb (g/dL)	≥13.6	450	4.0 (2-8.1)	5.1	7.6 (5.9-9.2)	
	12.5-13.5	195	4.7 (2.8-9.2)	6.5	16.8 (14.5-19.0)	
	10.1-12.4	239	7.8 (3.9-22)	10.6	10.6 (8.1-13.1)	
	≤10	25	11.0 (4.1-20)	16.8	19.2 (12.3-26.2)	<.001
6MWT (m)	400+	99	2.4 (1.3-4.8)	5.0	6.5 (2.9-10.0)	
	250-399	282	4.0 (2.0-7.0)	6.5	6.9 (4.8-9.0)	
	<250	211	5.6 (3.4-12.0)	11.3	10.5 (8.2-12.9)	
	Unable to walk	194	7.7 (4.0-17.0)	15.8	14.9 (12.2-17.4)	
	Not known	171	6.9 (3.6-16.0)	16.0	16.1 (13.5-18.8)	<.001
NT-pro-BNP (pg/mL)	<68	163	4.0 (1.5-6.8)	5.8	6.8 (4.0-9.6)	
	69-162	164	4.0 (2.0-6.6)	6.4	7.1 (4.4-9.8)	
	163-437	163	5.4 (3.3-11.0)	11.2	10.8 (8.1-13.5)	
	>437	162	9.2 (4.2-23.0)	19.0	15.1 (11.8-18.5)	
	Not known	305	5.6 (3.0-12.0)	11.7	13.4 (11.5-15.2)	<.001
Serum creatinine (μmol/L)	<106	480	4.6 (2.4-9.1)	7.9	9.7 (8.1-11.3)	
	107-177	377	5.4 (3.0-12.0)	10.2	10.6 (8.8-12.4)	
	>177	85	6.7 (3.2-18.0)	14.1	19.5 (15.7-23.3)	<.001
NYHA class	I	159	4.0 (1.8-7.7)	10.9	8.6 (5.9-11.3)	
	II	224	4.2 (2.5-9.2)	11.6	10.3 (8.7-11.8)	
	III	79	6.9 (3.8-15.0)	10.1	13.5 (11.4-15.7)	
	IV	118	8.0 (5.0-22.0)	11.1	13.9 (6.6-21.1)	.02
Ejection fraction (%)	40%-45%	225	4.8 (3.2-10.0)	11.0	11.1 (7.8-14.3)	
	30%-39%	265	5.1 (2.2-11.0)	10.7	11.7 (9.6-13.9)	
	<30%	116	5.0 (2.6-11.0)	11.2	9.7 (7.4-12.1)	
	Not known	349	5.0 (3.1-11.0)	11.1	11.1 (9.1-13.1)	0.6
LV impairment	Mild	241	4.8 (3.0-11.0)	8.1	11.0 (8.8-13.2)	
	Moderate	408	4.9 (2.6-9.8)	11.1	10.8 (9.0-12.5)	
	Severe	308	5.4 (2.8-12.0)	7.6	11.1 (9.1-13.5)	.9
Systolic BP (mm Hg)	<90	19	12.0 (6.6-27)	26.1	9.3 (2.4-16.2)	
	≥90	909	4.9 (2.6-10.0)	10.4	11.1 (9.9-12.2)	
	Not known	29	10.0 (4.0-18)	7.6	8.4 (1.8-15.0)	.7
Serum sodium (mmol/L)	<135	74	9.6 (3.9-20.0)	20.9	10.8 (6.7-14.8)	
	135-145	855	4.9 (2.7-10.0)	10.1	11.0 (9.8-12.2)	
	>145	13	4.2 (1.7-10.0)	9.1	11.3 (1.6-21.0)	.6

High-sensitivity CRP is shown as unadjusted and adjusted means. High-sensitivity CRP was adjusted for age, sex, white blood cell count, presence of diabetes mellitus, smoking, BBs, statins, and NSAIDs. *P* values relate to the significance within the overall group. *IQR*, Interquartile range; *Hb*, hemoglobin; *BP*, blood pressure.

Most patients were already taking angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB) (70%) and BB (51%) at the time of referral. All patients with LVSD who had no contraindications or intolerance were subsequently started on these agents. Of the 402 followed at 1 year, 93% were taking ACEi/ARB and 84% BB.

Patients with heart failure and LVSD had a higher mean hsCRP value (10.9 ± 18.0 mg/L) despite the exclusion of patients with infection or an inflammatory disease when compared with those who had no heart failure (7.9 ± 12.1 mg/L, $P < .001$). Patients who survived to a second assessment had a lower mean hsCRP value of 7.7 ± 15.8 mg/L at 1 year.

Over a follow-up period of 36 months, 163 (17.0%) of 957 patients with LVSD died. Patients with values in the highest quartile of hsCRP had the worst prognosis (Figure 2). A multivariable analysis was performed to analyze the relationship of hsCRP to other variables in this population (Table II). More severe NYHA class, shorter distance covered during a 6MWT, anemia, higher plasma concentrations of NT-pro-BNP, and renal dysfunction were all associated with higher concentrations of CRP. No relationship was observed between CRP and LV function, assessed qualitatively or by a calculated LVEF.

In a Cox regression model, hsCRP, NT-pro-BNP, serum creatinine, and 6MWT were all strong independent predictors of survival but not NYHA class, LV function, anemia, or hyponatremia (Table III).

We compared the performance of NT-pro-BNP as a prognostic indicator against hsCRP using a receiver operating characteristic curve analysis. Only those patients who had both hsCRP and NT-pro-BNP at baseline were included in this analysis (n = 652, 68%). NT-pro-BNP was superior to hsCRP ($P < .05$) with an area under the curve of 0.74 (95% CI 0.68-0.84) compared to hsCRP's 0.67 (95% CI 0.61-0.74).

Table III. A Cox regression model of prognostic variables

Variable		Hazard ratio (95% CI)	P
HsCRP (pg/mL)	2.8-5	1.5 (0.8-2.9)	
	5.1-11	1.8 (1.2-2.8)	
	>11	3.0 (2.1-4.1)	<.001
NT-pro-BNP (pg/mL)	69-162	1.2 (0.5-2.9)	
	163-437	1.5 (0.8-2.8)	
	>437	5.3 (3.4-8.4)	
	Not known	2.1 (1.5-3.0)	<.001
6MWT (m)	250-399	2.9 (0.7-12.4)	
	<250	3.7 (1.6-8.2)	
	Unable to walk	4.1 (2.3-7.3)	
	Not known	2.3 (1.4-3.9)	<.001
SBP (mm Hg)	>90	1.9 (0.5-7.6)	
	Not known	2.8 (1.0-7.6)	.09
NYHA class	II	1.1 (0.7-1.9)	
	III	2.2 (1.6-3.2)	
	IV	1.6 (0.7-4.1)	<.001
LV impairment	Moderate	1.3 (0.8-2.0)	
	Severe	1.6 (1.2-2.4)	.011
Ejection fraction (%)	30-39	1.4 (0.8-2.6)	
	<30	1.0 (0.7-1.6)	
	Not known	1.0 (0.7-1.4)	.6
Hb (g/dL)	12.5-13.5	1.7 (1.2-2.5)	
	10.1-12.4	0.9 (0.6-1.3)	
	≤10.0	1.1 (0.5-2.5)	.09
Creatinine (μmol/L)	107-177	1.8 (1.3-2.6)	
	177+	2.7 (1.8-4.1)	<.001
Sodium (mmol/L)	≥146	1.8 (0.6-4.9)	
	<135	0.7 (0.3-1.6)	.6

Hazard ratios are shown with CIs for each prognostic factor. *P* values relate to the significance between the hazard ratios for that prognostic factor. High-sensitivity CRP was adjusted for age, sex, white blood cell count, presence of diabetes mellitus, smoking, BBs, statins, and NSAIDs. *SBP*, Systolic blood pressure.

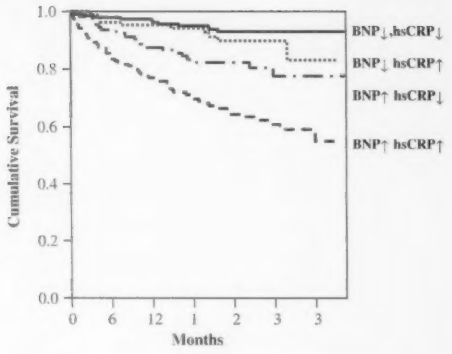
Patients who had elevations of both NT-pro-BNP and hsCRP had a much worse prognosis than those who had both values below median and both carried independent prognostic value (Figure 3).

We analyzed the data from 402 patients with systolic impairment known to be free of inflammatory disease or infection that had a repeat assessment 1 year later, which showed that 217 (54%) had a change in hsCRP category. Change in hsCRP over the 1-year period (ΔhsCRP) was compared with change in hemoglobin, serum creatinine, and ejection fraction. A rise in ΔhsCRP was associated with a fall in hemoglobin over the same period, but no change was noted between ΔhsCRP and the other variables (Table IV).

Discussion

This study demonstrates that in patients with LVSD, an increased hsCRP is associated with poorer functional capacity and an adverse outcome independent of other prognostic markers. It also describes changes in hsCRP over the following year and their relationship to other measures of disease progression. These data suggest that

Figure 3



HsCRP	BNP	0 months	12 months	24 months	36 months
No	No	195 (5)	149 (6)	62 (0)	5 (0)
No	Yes	104 (5)	85 (3)	49 (1)	2 (0)
Yes	No	143 (14)	109 (3)	66 (2)	8 (1)
Yes	Yes	152 (26)	106 (15)	58 (1)	11 (0)

Kaplan-Meier curve of survival according to hsCRP and BNP values. In the table, values are expressed as the number of patients at risk (number of patients who died).

hsCRP, a simple and widely available test, might be useful in clinical practice either to identify patients with an adverse outcome or, potentially, as a new target for specific therapy. Clearly, much further research is required to reveal the full potential of hsCRP for the assessment of patients with heart failure.

There is mounting evidence that an inflammatory process exists in heart failure that could be one of the mechanisms driving disease progression, making it a potential target for treatment. Recent trials with anti-inflammatory therapies such as the TNF-α antagonists etanercept and infliximab were disappointing, but this may be because of inadequate patient selection.[9] Patients who had a worse functional capacity and NYHA class, cardiac cachexia, or decompensated heart failure despite standard therapy are likely to have activation of cytokine/inflammatory systems and should be targeted in such trials. C-reactive protein, which is stimulated by IL-6, is a widely available marker of inflammation that may be useful in selecting patients for anticytokine therapies, and as evidence, that therapy has modified the process.[3,10]

Although increases in hsCRP were related to many other adverse prognostic features including NYHA class, serum creatinine, and BNP, it retained independent prognostic value. This provides circumstantial evidence that inflammation may help drive the progression of heart failure. Conclusive evidence awaits the identification of an anti-inflammatory intervention that alters

Table IV. Change in hsCRP over a 1-year period expressed as ΔCRP compared to other prognostic variables

ΔCRP (mg/L)	>−11	−11 to −2.9	−2.8 to 2.8	2.9 to 11	>11	P
ΔHemoglobin (g/dL)	−0.1 (−0.6 to 0.7)	−0.3 (−1 to 0.6)	−0.5 (−1 to 0.2)	−0.7 (−2.2 to 0.2)	−1.1 (−2.2 to 0.6)	<.001
n	43	69	217	50	23	
ΔCreatinine (μmol/L)	13 (−9 to 43)	9 (−2 to 25)	6 (−2 to 20)	6 (−4 to 23)	5 (−12 to 26)	NS
n	43	69	217	50	23	
ΔEF (%)	11 (−7 to 18)	8.5 (0 to 15)	9 (0 to 13)	5 (1 to 13)	3 (1 to 14)	NS
n	19	28	105	23	7	

Values are expressed as median (IQR). *P* values were calculated using Kruskal-Wallis test. *NS*, Not significant.

outcome. We failed to show a relationship between hsCRP and LVEF either at baseline or at 1 year, suggesting that inflammatory processes may not be a major determinant of cardiac dysfunction. The link between cytokines and progression of heart failure may be due to effects on peripheral organs including skeletal muscle, bone marrow, blood vessels, liver, and kidneys.

Our study also shows that, as for patients with coronary artery disease,[11,12] inflammatory markers may rise or fall in the long term. Treatments for heart failure, including BBs, ACEi's, and ARBs have anti-inflammatory properties and reduce CRP levels and could have accounted for some of the observed change.[7,13,14] However, short-term variation of hsCRP may also occur. If so, this might reduce its prognostic power, perhaps especially in longer-term follow-up. Indeed, hsCRP seemed a better predictor of near-term events, which might be an advantage for monitoring disease progression.

Increases in hsCRP were associated with a greater fall in hemoglobin. Anemia is common in patients with heart failure and associated with worse symptoms and increased mortality.[15] Patients with anemia in our study had higher hsCRP levels, and there was an inverse relationship between changes in hsCRP and hemoglobin. It is likely that the anemia of chronic heart failure is multifactorial and may be due, in part, to increases in inflammatory cytokines. Activation of reticuloendothelial cells and cytokines such as TNF-α, IL-6, and IL-1B can alter iron homeostasis, reduce the production of erythroid progenitor cells and erythropoietin, and shorten the life span of red cells, leading to anemia.[16]

Renal dysfunction is also common in heart failure and is related to a poor prognosis and anemia.[17] Patients with renal dysfunction also had elevated hsCRP in our study. It is possible that inflammation provides an important link between anemia and renal dysfunction.

N-terminal pro-B natriuretic peptide was a better prognostic marker than CRP with a greater sensitivity and specificity, but the combination was significantly better than either alone. Development of multivariable prognostic models could help target expensive treatments more effectively. This study suggests that hsCRP might be a useful addition to a prognostic model including NT-pro-BNP, serum creatinine, the severity of symptoms, and functional limitation.

Further trials of anti-inflammatory therapies are merited in this area as, despite recent advances, heart failure is a major and growing public health problem. Statins are an obvious choice for lowering hsCRP. Whether statins are safe and effective for patients with heart failure is being addressed by 2 trials, CORONA and GISSI-CHF,[18] although these trials may not be able to determine which of the several effects of statins are responsible.

Limitations to the study

There are several limitations to the study. Firstly, it was performed in a single hospital clinic serving a large local community. The patients managed in this service might differ from those either in primary care or in tertiary care centers. However, the inclusion of a large proportion of all available patients in one geographic region may be more epidemiologically representative than recruiting patients from a large number of centers but only a small proportion of those available, as is common in clinical trials. There are missing values to the some of the tests performed because of patient inability or refusal to undergo the test (6MWT) or to loss of blood samples. Different criteria for the diagnosis of diastolic heart failure may have increased the reported prevalence of this condition.

Conclusions

High-sensitivity CRP is a widely available, prognostically useful marker of inflammation in patients with heart failure. Inflammation may be an important mechanism of the progression of heart failure. Trials targeting patients with increased hsCRP with agents likely to reduce inflammation are warranted.

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Long-term effect of atorvastatin on neurohumoral activation and cardiac function in patients with chronic heart failure: A prospective randomized controlled study

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Background Statins have pleiotropic effects, such as improvement in endothelial function and antiinflammatory, antiproliferative, and antioxidative effects, that should be beneficial for patients with chronic heart failure (CHF). The aim of this study was to investigate the long-term effect of statins on neurohumoral activation and cardiac function in patients with CHF.

Methods We enrolled 38 outpatients with mild to moderate CHF and radionuclide left ventricular ejection fraction (LVEF) <40%. These patients were randomly assigned to receive atorvastatin (10 mg/d) or conventional treatment for heart failure and were prospectively followed up for at least 3 years. At entry, we measured plasma concentrations of brain natriuretic peptides (BNPs) and left ventricular end-diastolic dimension and LVEF by echocardiography; thereafter, these measurements were repeated at least every 6 months. The primary end point was defined as the improvement in cardiac function and BNP.

Results There were no significant differences in age, sex, New York Heart Association class, left ventricular end-diastolic dimension, LVEF, and serum cholesterol level at entry between patients with (n = 19) and without atorvastatin (control, n = 19). After a follow-up period of 31 ± 14 months, BNP (median [25th, 75th percentile]) significantly decreased in the atorvastatin group (84 [36, 186] to 55 [37, 91] pg/mL, $P = .02$) but not in the control group. Left ventricular end-diastolic dimension significantly decreased (67.1 [59.9, 70.8] to 61.1 [58, 63.9] mm, $P = .02$), and LVEF also significantly increased in the atorvastatin group (33.3% ± 7.4% to 39.1% ± 12.1%, $P = .01$) but not in the control group.

Conclusion Long-term atorvastatin therapy decreases neurohumoral activation and improves cardiac function in patients with mild to moderate CHF. (Am Heart J 2007;153:1055.e1-1055.e8.)

Effects of exercise training on heart rate recovery in patients with chronic heart failure

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Background Heart rate recovery (HRR) is a marker of vagal tone that is associated with survival, but little is known about the effects of exercise training on HRR in patients with heart failure (HF).

Methods Twenty-four patients with HF were randomized to a 2-month residential rehabilitation program or to usual care. Symptom-limited exercise testing was performed at baseline and at discharge from the program. Heart rate recovery was expressed as the decline in heart rate from peak exercise through 6 minutes into recovery. In addition, HRR recovery curves were normalized to a range of 1 at peak heart rate and 0 at 6 minutes and adjusted for differences in heart rate reserve, facilitating the comparison of recovery curve shapes between groups.

Results Mean peak oxygen uptake and oxygen uptake at the lactate threshold increased 26% ($P < .05$) and 39% ($P < .001$), respectively, in the exercise group, whereas neither of these responses changed significantly among controls. Heart rate recovery was significantly more rapid in the exercise group after training (main effect 12.6 vs 2.6 beat/min in the trained and control groups, respectively, $P = .005$). The normalized curves showed that the largest improvement in recovery curve shape occurred in the exercise group, but most of the HRR improvement was accounted for by a widening of the difference between peak and resting heart rate.

Conclusion Exercise training results in a faster HRR in patients with HF. Heart rate recovery, as a simple marker of autonomic function, is an easily acquired response that may be useful for evaluating patient outcomes in cardiac rehabilitation. (Am Heart J 2007;153:1056-63.)

Autonomic nervous system (ANS) imbalance is associated with mortality in patients with cardiovascular disease.[1] The heart rate response to, and recovery from, a bout of exercise is mediated by the dynamic interaction between the sympathetic and parasympathetic components of the ANS.[1,2] Specifically, greater sympathetic tone predominates as heart rate increases during exercise, and vagal reactivation mediates the rate at which heart rate recovers after exercise. A growing body of studies in recent years has shown that the rate at which heart rate recovers from exercise (termed *heart rate recovery*, or *HRR*) is associated with all-cause and cardiovascular mortality.[1,3-6]

The better survival associated with a more rapid HRR is thought to reflect higher vagal tone commonly linked to better fitness and cardiovascular health.[1] A particularly large number of recent studies have demonstrated an association between autonomic imbalance and poor outcomes in patients with chronic heart failure (HF).[7,8] In addition to the numerous physiologic benefits of cardiac rehabilitation in patients with HF, exercise training has been associated with higher vagal tone.[9-11] However, the application of HRR as a marker for improved cardiovascular health in the context of cardiac rehabilitation has not been fully explored. Heart rate recovery could potentially represent a simple, noninvasive tool to identify high-risk patients and assess patient outcomes during cardiac rehabilitation.

Previous studies on HRR have generally compared only the heart rate at a given point in recovery (eg, 1 or 2 minutes) before and after training or between patients with favorable versus poor outcomes. Some investigators have theorized that the transition processes from sympathetic control of heart rate at peak exercise to vagally mediated heart rate at rest is reflected in the shape of the HRR curve, providing additional insight into autonomic balance and the degree of risk.[12-14] Previous studies investigating the effects of exercise training on HRR have not incorporated the potentially important information contained in the entire recovery period. In addition, it is well known that training widens the heart

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Table I. Baseline characteristics

	Exercise group (n = 12)	Control group (n = 12)
Age (y)	56 ± 5	55 ± 7
Height (cm)	173 ± 7	169 ± 5
Weight (kg)	76.9 ± 7.5	71.5 ± 10.2
Ejection fraction (%)	31.5 ± 6.7	34.6 ± 4.1
Forced vital capacity (% normal)	88.8 ± 11	84.2 ± 20
Medications (n)		
Digoxin	8	6
ACE inhibitor	12	11
Diuretic	6	6
Other	3	5
MI (n)		
Anterior	6	6
Inferior	4	3
Posterior	2	2
Risk factor (n)		
Smoking	11	10
Diabetes mellitus	1	0
Hyperlipidemia	7	4
Hypertension	7	4
Family history of CAD	7	8
Procedure (n)		
PCI	2	1
CABS	9	10

ACE, Angiotensin-converting enzyme; *CAD*, coronary artery disease; *PCI*, percutaneous coronary intervention; *CABS*, coronary artery bypass surgery.

rate reserve (the difference between peak and resting heart rate), which has been suggested to have a significant effect on HRR and the shape of the HRR curve.[12,15,16] The purpose of the current study was to characterize the effects of a concentrated, high-intensity residential exercise training program on HRR and the shape of the HRR curve in patients with HF.

Methods

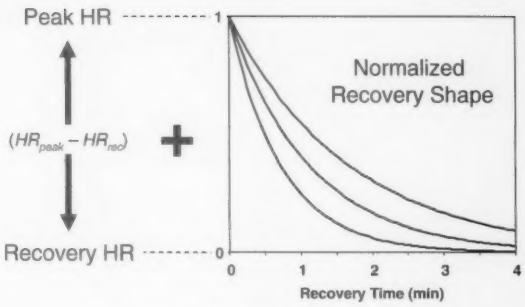
Patients

Twelve male patients (mean age 56 ± 5 y) were randomized to an exercise group, and 12 male patients (mean age 55 ± 7 y) were randomized to a control group (Table I). All had sustained a myocardial infarction (MI), and the hospital course in all patients included the diagnosis of HF. The presence of HF was documented by signs, symptoms, and an angiographically determined ejection fraction <40%. All were limited by fatigue or dyspnea on baseline exercise testing, and none had clinical evidence of pulmonary disease. Written informed consent was obtained, and all patients had stable symptoms for at least 1 month before randomization.

Exercise training

After stabilization and initial testing, patients in the exercise group resided in a rehabilitation center in Seewis, Switzerland, for a period of 8 weeks. The center has its own staff of physicians, consisting of a medical director and 3 interns/residents. Program components included education, exercise,

Figure 1



Example of the calculation of the normalized HRR curves.

and low-fat meals prepared by the center's cook. Two outdoor walking sessions daily for a duration of approximately 1 hour were performed, once in the morning and once in the afternoon. To facilitate monitoring, walking groups were stratified into 4 levels based on clinical status, exercise capacity, and performance on a 500-m walking test (50-m increase in altitude) on a nearby hill. Target exercise heart rates were individualized and monitored for each subject. The patients were accompanied by a physician and exercise leaders during these walking sessions. A van equipped with emergency equipment remained near the group.

In addition to these walking periods, the patients performed four 45-minute periods of monitored stationary cycling per week. The cycling sessions were designed to elicit an intensity of roughly 60% to 80% of the patient's heart rate reserve and were increased progressively as tolerated. Control patients received usual care.

Exercise testing

Before randomization, each patient performed a preliminary exercise test to help ascertain clinical stability and to habituate the patients to the testing procedure and gas exchange apparatus. Maximal exercise testing was performed on an electrically braked cycle ergometer using an individualized ramp protocol. Briefly, this test entailed choosing an individualized ramp rate to yield a test duration of approximately 10 minutes.[17] A 12-lead electrocardiogram was monitored continuously, and blood pressure was measured manually every minute during exercise and throughout the recovery period. The patient's subjective level of exertion was quantified every minute using the Borg 6-20 scale.[18] All tests were continued to volitional fatigue/dyspnea; no patients were limited by angina.

Respiratory gas exchange variables were acquired continuously throughout exercise using the Schiller CS-100 metabolic system (Baar, Switzerland). The gas exchange data were obtained breath-by-breath and expressed as rolling 30-second averages printed every 10 seconds. Blood was sampled each minute using an indwelling arterial catheter, and plasma was separated immediately for analysis. The lactate threshold was determined visually by consensus between 2 experienced reviewers (blinded to group and pre-/posttest identity) using a computerized plot of the oxygen uptake versus lactate relationship.

Table II. Exercise test responses (mean ± SD)

	Exercise group (n = 12)		Control group (n = 12)		
	Baseline	**Post**	**Baseline**	**Post**	**P***
Rest					
Heart rate (beat/min)	84 ± 17	73 ± 16	8 ± 13	79 ± 15	.84
Systolic BP (mm Hg)	128 ± 15	131 ± 13	128 ± 20	124 ± 22	.46
Diastolic BP (mm Hg)	73 ± 12	74 ± 10	74 ± 12	68 ± 10	.28
Lactate threshold					
Heart rate (beat/min)	117 ± 18	113 ± 19	115 ± 16	107 ± 13	.70
Systolic BP (mm Hg)	152 ± 20	161 ± 14	157 ± 25	148 ± 19	.18
Diastolic BP (mm Hg)	85 ± 13	82 ± 18	84 ± 12	79 ± 12	.77
Oxygen uptake ($mL \cdot kg^{-1} \cdot min^{-1}$)	13.6 ± 2.8	18.9 ± 2.3†	13.5 ± 3.1	11.5 ± 1.9	<.001
Oxygen uptake (L/min)	1.063 ± 0.233	1.437 ± 0.199†	0.963 ± 0.243	0.829 ± 0.160	<.001
Minute ventilation (L/min)	31.8 ± 7.0	40.4 ± 6.0‡	28.9 ± 7.9	24.2 ± 3.8	.001
V_{CO_2} (mL/min)	952 ± 237	1329 ± 225‡	956 ± 366	735 ± 157	<.001
RER	0.89 ± 0.09	0.92 ± 0.06	0.97 ± 0.14	0.90 ± 0.07	.11
Workload (watts)	69.7 ± 18	105.1 ± 17†	64.2 ± 28	56.2 ± 15	.001
Perceived exertion	10.5 ± 2.4	9.7 ± 1.6	11.2 ± 2.2	11.3 ± 1.7	.40
Maximal exercise					
Heart rate (beat/min)	144 ± 23	151 ± 24	141 ± 18	139 ± 16	.46
Systolic BP (mm Hg)	170 ± 24	178 ± 24	175 ± 30	174 ± 23	.51
Diastolic BP (mm Hg)	86 ± 14	87 ± 18	89 ± 11	90 ± 17	.99
Oxygen uptake ($mL \cdot kg^{-1} \cdot min^{-1}$)	19.7 ± 3.2	24.8 ± 4.7‡	18.8 ± 4.3	18.8 ± 4.6	.04
Oxygen uptake (L/min)	1.513 ± 0.258	1.873 ± 0.396‡	1.334 ± 0.284	1.323 ± 0.310	.05
Minute ventilation (L/min)	65.1 ± 12.3	78.5 ± 10.8‡	52.1 ± 10.9	49.7 ± 11.7	.02
V_{CO_2} (mL/min)	1792 ± 321	2261 ± 444‡	1644 ± 366	1562 ± 418	.02
RER	1.19 ± 0.13	1.21 ± 0.06	1.23 ± 0.12	1.18 ± 0.12	.23
Workload (watts)	129.0 ± 21	171.9 ± 28†	115.2 ± 28	117.4 ± 32	.01
Perceived exertion	18.7 ± 0.98	18.9 ± 0.90	19.0 ± 0.95	18.7 ± 0.98	.30
Exercise time (min)	9.4 ± 1.7	12.3 ± 1.7†	9.0 ± 2.2	9.1 ± 1.7	<.01

BP, Blood pressure; *RER*, respiratory exchange ratio.
*Represents *P* value from group/test interaction.
†$P < .01$, versus baseline within group.
‡$P < .05$, versus baseline within group.

Heart rate recovery

Heart rate was measured supine, standing, during each minute of exercise, at maximum exercise, and during active recovery (zero load) at minutes 1 through 6. The HRR curves were divided into 2 elements: a normalized recovery curve that characterizes how quickly peak heart rate (HR_{peak}) recovers to a posttest resting rate and an amplitude scaling term defined by the difference between HR_{peak} and the postexercise resting heart rate as described previously.[12] This is illustrated in Figure 1. To compare the shape of the normalized recovery curves, HRR was standardized to a uniform range of 1.0 at HR_{peak} and zero at 6 minutes into recovery (HRR_6). Heart rate recovery at 6 minutes into recovery was subtracted from each HRR value, and the difference was divided by ($HR_{peak} - HRR_6$). This normalization process supports the comparison of the shape of the recovery curve independent of the amplitude scaling factor related to changes in peak and resting heart rates.

Statistics

NCSS (NCSS, Kayesville, UT) was used to perform multivariate analysis of variance (ANOVA) procedures comparing exercise, recovery, and ventilatory gas exchange responses between groups. This procedure considered both inter- and intragroup comparisons and interactions among the factors (group and test) for each dependent variable. Post hoc multiple comparison procedures were performed using the Bonferroni method. Clinical and demographic data were compared using unpaired *t* tests and χ^2 analyses. Normalized HRR curves between exercise and control groups were compared using multivariate ANOVA with group and test as independent factors. Data are expressed as mean ± SD.

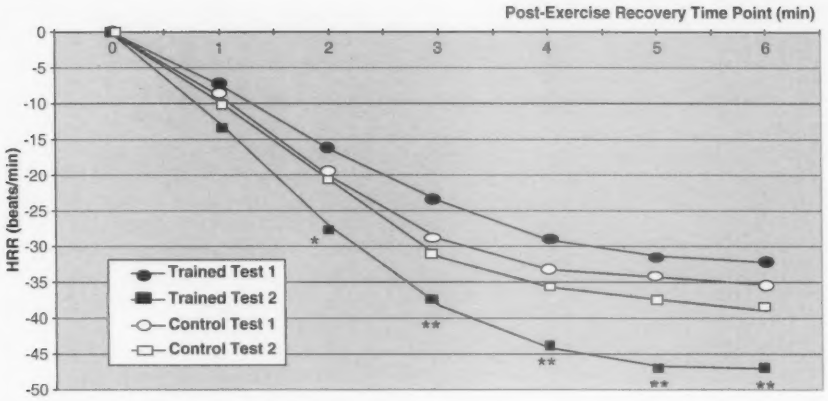
Results

No differences were observed between groups initially in clinical or demographic data, including age, height, weight, resting blood pressure, pulmonary function, ejection fraction, or maximal oxygen uptake (Table I).

Maximal exercise testing

Both groups achieved maximal respiratory exchange ratios of approximately 1.20 and perceived exertion levels of approximately 19 on both tests, suggesting that maximal efforts were generally achieved (Table II). No patient in either group was limited by angina, and none exhibited electrocardiographic evidence of ischemia during baseline exercise testing. The exercise group

Figure 2



** P < .05, ** P < .01 within group*

The effects of exercise training on HRR in the trained and control groups.

demonstrated a 29% increase in maximal oxygen uptake (19.7 ± 3.2 to 24.8 ± 4.7 mL·kg^{-1}·min^{-1}, $P = .04$ between groups). Concomitant increases in maximal minute ventilation, CO_2 production, exercise time, and watts achieved were observed in the exercise group. No differences between tests were observed among control patients in maximal oxygen uptake, exercise time, or watts achieved.

Oxygen uptake at the lactate threshold increased by 39% in the exercise group, whereas a small decrease was observed among controls ($P < .001$ between groups). Similar increases in exercise time and watts achieved at the lactate threshold were observed among patients in the exercise group, whereas no differences were observed in these responses in the control group. No differences were observed within or between groups for heart rate, systolic or diastolic blood pressure, respiratory exchange ratio, or perceived exertion at this point.

Heart rate recovery

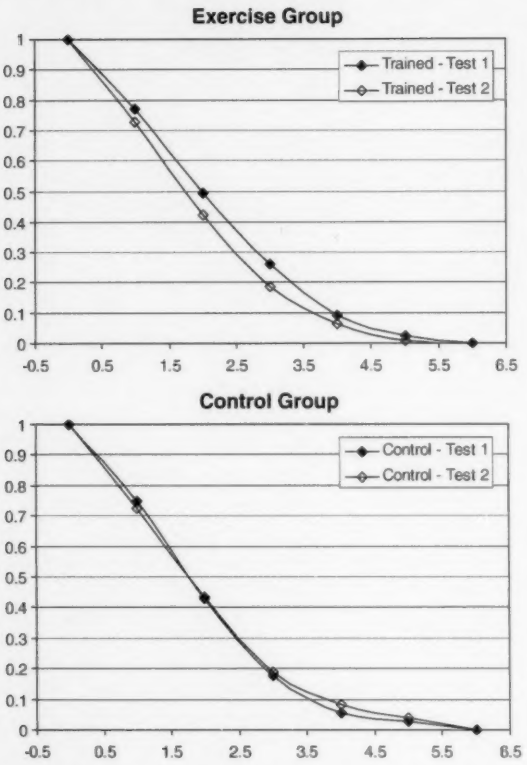
Heart rate recovery was significantly faster in the exercise group for minutes 2 to 6 after training (ANOVA main effect in trained subjects 12.6 beats/min, $P < .001$; main effect among controls 2.6 beats/min, $P = .27$; between-group interaction $P = .005$; pooled variance 15.7 beats/min). Among trained subjects, the faster HRR was more pronounced as the recovery period progressed; heart rate was 5.4, 10.9, 14.6, 15.1, 15.4, and 14.8 beats/min lower at minutes 1 through 6, respectively, after training in the exercise group. Heart rate in the control group did not change significantly at any of the individual minutes in recovery (Figure 2).

The exercise group was characterized by a slight but systematic increase in the slope of the normalized recovery curve (ie, faster recovery) after training, evident at 1 minute and continuing throughout the recovery period (change in overall slope 0.72 to 0.76, not significant) Figure 3). Among control subjects, the curves for the pre- and posttests were closely matched throughout recovery (slopes 0.75 and 0.75 for the pre- and posttests, respectively). At 2 minutes, the normalized curve improved from 0.51 to 0.44 for the exercise group and remained unchanged among controls (0.57 to 0.57). Multiplying the difference in the normalized shapes by the scaling term ($HR_{peak} - HRR_6$) from test 2 provided an estimate of the contribution to improving HRR from changes in the shape of the recovery curve.[12] Table III summarizes the results for HRR at 2 minutes. Thirty percent of the improvement in HRR for the exercise group was contributed by an improvement in the shape of the recovery curve, whereas there was no contribution to HRR by the change in the shape of the curve among controls. The remaining difference in HRR between the pre- and posttests (70% for the exercise group) was the result of a widening of the heart rate reserve (reduced resting heart rate and higher HR_{peak} between the baseline and 2-month exercise tests).

Discussion

The ability of heart rate to recover after exercise is related to the capacity of the cardiovascular system to reverse ANS (withdrawal of vagal activity) and baroreceptor (detection of changes in blood pressure

Figure 3



Normalized HRR responses in the exercise (top) and control (bottom) groups for minutes 1 to 6 in recovery. The differences in the shapes of the curves did not differ within or between groups.

and inhibition of sympathetic discharge) adaptations that occur during exercise, often termed *vagal reactivation*.[13,19] The association between HRR and cardiovascular health is underscored by the long-established observation that recovery of heart rate is faster in athletes[13] and the fact that autonomic imbalance, principally a deficiency in vagal tone, is associated with mortality.[1,8,11] Presumably because of impaired vagal reactivation, HRR has been widely recognized in recent years as a powerful marker of prognosis in patients with cardiovascular disease.[3-6,20] Because of the strong association between HRR and mortality,[3-6,12,20] and the link between HRR and exercise capacity or physical activity patterns,[1,11,21] HRR has the potential to be an additional marker of training efficacy and risk stratification in patients undergoing cardiac rehabilitation.

In the current study, a sizable training effect was evidenced by 26% and 39% increases in Vo_2 at peak exercise and the lactate threshold, respectively, whereas controls showed no changes in exercise capacity. These adaptations were larger than in most previous studies on HF,[22] which is likely explained by the comparatively high training stimulus associated with the residential program. The improvement in exercise capacity was associated with a more rapid HRR after training; the ANOVA main effect from minutes 1 to 6 in recovery was a reduction of 13 beats/min, with HRR $\approx$ 15 beats/min faster at minutes 3 through 6. This degree of improvement in HRR would have a marked effect on mortality risk based on recent studies.[1,3-6] We recently observed a 3% reduction in all-cause mortality per (faster) beat at 2 minutes in recovery.[23] The present results therefore suggest that training may have a considerable effect on outcomes in patients with HF via altered vagal modulation. The fact that the improvement in HRR among patients randomized to the exercise training group was correlated with the degree of increase in peak Vo_2 ($r = 0.59$ at 2 minutes, $P = .04$) and the increase in Vo_2 at the lactate threshold ($r = 0.70$, $P = .03$) further suggests a link between aerobic capacity and HRR.[1,11,21]

Comparison of HRR curves

Previous studies addressing the association between HRR and mortality have generally been limited to a single time point in recovery (eg, 1 or 2 minutes) and have ignored the potentially important information contained in the shape of the HRR curve. To our knowledge, no studies have assessed the effects of *training* on the HRR curve. In theory, a curve fit to HRR data offers the potential to both minimize the error associated with a single estimate and to leverage information that may be contained in the overall shape of the curve. Because it has recently been suggested that recovery heart rate is significantly affected by heart rate reserve (eg, a rapid HRR is associated with a comparatively low resting heart rate higher heart rate achieved),[12,15,16] we were interested in the effect training would have on the relation between heart rate reserve and HRR. We therefore decomposed HRR into 2 elements: a normalized recovery curve that defines how quickly HR_{peak} recovers to a stable posttest resting rate and an amplitude term defined by the difference between peak and resting recovery heart rate ($HR_{peak} - HRR_6$).[12] This decomposition provided a method to uniformly compare HRR curve shapes for patients with significantly different heart rate reserves.

Training increased HR_{peak} by 7 beat/min and decreased supine resting heart rate by 11 beat/min in the exercise group (a widening of 18 beat/min in the heart rate reserve). The comparison changes in the control group were a decrease of 2 beat/min at peak exercise and a decrease of 9 beat/min at rest (a widening of 7 beat/min in the heart rate reserve). Although the normalized HRR curve was slightly more rapid after

Table III. Contributions to HRR at 2 minutes from changes in normalized recovery shape and amplitude scaling associated with a widening range between peak and resting heart rate

	HRR (2 min)			Peak HRR (6 min)		Contributions to increasing HRR (2 min)			
						Shape		Scaling	
Group	Test 1	Test 2	Increase	Test 1	Test 2				
Exercise	16.3	27.2	10.8	32.2	47.0	3.3	30%	7.5	70%
Control	20.1	22.0	1.9	35.3	38.9	−0.2	−9%	2.1	109%

In the exercise group, recovery curve shape changes accounted for a larger percentage of the contribution to total HRR relative to the control group. The largest contribution to improving HRR for both groups was increasing amplitude scaling.

training in the exercise group, the fact that the curves did not differ between the exercise and control groups (Figure 3) suggests that the improved HRR after training (Figure 2) is largely attributable to the wider heart rate reserve observed in the trained group. By normalizing HRR and using a scaling term throughout the recovery period ($HR_{peak} - HRR_6$),[12] we observed that 70% of the change in HRR was attributable to a greater heart rate reserve after training. This is in accordance with the observations of Desai et al,[15] who reported that abnormal HRR in patients with coronary artery disease was explained almost entirely by an impaired heart rate response *during* exercise. Similarly, Racine et al[16] reported that when HRR was normalized by heart rate reserve, there was virtually no difference between healthy subjects and patients with HF; HR_{peak} achieved appeared to be the primary determinant of HRR. Hadley et al[12] also observed that HRR was strongly correlated with heart rate reserve. In a multivariate model, none of several HRR measurements were significant predictors of either cardiovascular or all-cause mortality; only heart rate reserve was associated with these outcomes.

The comparison of HRR curves in the present study was novel and requires confirmation by larger randomized trials. Our findings suggest that the improvement in HRR after training is attributable at least in part to a widening of the heart rate reserve but do not negate the potential influence of training on autonomic balance. An increase in vagal tone after training is implied by the reduction in resting heart rate, and the higher HR_{peak} suggests enhanced sympathetic drive, lowered vagal influence, or both at peak exertion. These results indicate, however, that heart rate reserve should be considered when applying HRR to assess the effects of training or stratifying risk in patients with cardiovascular disease.

Previous studies on training and HRR

The effects of training on autonomic tone, baroreflex sensitivity, and heart rate variability (HRV) have been widely studied in animal models, and these studies suggest that exercise training provides a nonpharmacologic benefit to cardiac autonomic control.[9,24-26] In conscious dogs, training increases HRV and baroreflex sensitivity and reduces the susceptibility to experimentally-induced ventricular fibrillation.[26,27] Numerous investigators have observed that exercise training in patients with cardiovascular disease increases HRV.[11,28] Baroreflex sensitivity, measured using heart rate and systolic blood pressure variability after phenylephrine infusion or by the spontaneous baroreflex technique, has been shown to increase after programs of cardiac rehabilitation.[29,30] However, no studies to our knowledge have reported changes in HRR along with these indices of autonomic function before and after training.

Although faster HRR has long been associated with higher levels of fitness,[31] few data are available regarding HRR in patients with cardiovascular disease undergoing training. Tiukinhoy et al[32] observed that HRR was 18 beats/min faster 1 minute into recovery after 12 weeks of rehabilitation among patients after a cardiac event. Hao et al[33] reported modest (3-6 beats/min) improvements in HRR 1 minute into recovery (using a walking cool-down protocol) among both elderly and younger patients referred to a 12-week rehabilitation program. Kligfield et al[34] demonstrated that 1-minute-postexercise HRR was more rapid (by 2-4 beats/min) in response to submaximal activity after 12 weeks of rehabilitation. Streuber et al[35] reported that HRR 1 minute postexercise improved by 5 beats/min after 12 weeks, but the improvement was only observed among those with the lowest initial exercise capacity. Similarly, Giallauria et al[36] reported that HRR 1 minute postexercise improved by approximately 6 beats/min after 3 months of training after MI. To our knowledge, the recent study of Dimopoulos et al[37] is the only analysis of training and HRR in patients with HF. Heart rate recovery was compared between subjects randomized to 36 sessions of continuous (n = 14) or interval (n = 10) training. At 1 minute postexercise, HRR improved (by 9 beats/min) only among subjects in the continuous training group, whereas HRR in the interval group did not differ between evaluations. Similar to these previous studies, we observed an improvement of 5.4 beats/min at 1 minute into recovery after training; however, a more dramatic improvement in HRR occurred later into recovery, with training having an overall improvement on HRR of ≈13 beats/min

(Figure 1). Differences between these studies may be explained by differences in HRR measurement points, whether patients performed a cool-down walk, and the training stimulus used.

Limitations

Our study sample size was small and included only patients with HF with an ischemic etiology after MI or bypass surgery; the responses may not be applicable to the wider population of patients with HF. In addition, the training program was intensive, and the adaptations we observed in our residential program may not occur in more conventional outpatient programs.

Summary

Heart rate recovers more rapidly after exercise after a concentrated, intensive program of exercise training in patients with HF. Most of the improvement in HRR was associated with a widening of the difference between resting and peak exercise heart rate. Nevertheless, HRR, as a simple marker of autonomic function, is an easily acquired response that may be useful in identifying high-risk patients and for evaluating patient outcomes in cardiac rehabilitation.

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Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in patients with congestive heart failure and chronic kidney disease

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Background Patients with coexistent heart failure and chronic kidney disease (CKD) have a poor prognosis, possibly related to the underuse of standard medical therapies—angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB).

Methods We performed a retrospective analysis of the Minnesota Heart Survey, identifying patients hospitalized in 2000 in the Minneapolis–St Paul metropolitan area with heart failure. The main outcome measure was the association of ACE-I and ARB use on 30-day and 1-year mortality, stratified by glomerular filtration rate (GFR).

Results Compared to patients with heart failure with preserved renal function (GFR ≥90 mL/min), patients with severely impaired renal function (GFR <15 mL/min) were far less likely to receive ACE-I or ARB during hospitalization (52.0% vs 69.5%, $P < .0001$) or at discharge (50.5% vs 65.1%, $P < .0001$). Worsening renal function was associated with increased mortality, both at 30 days and at 1 year. The inhospital use of either an ACE-I or ARB was associated with significantly reduced 30-day mortality (OR 0.45, 95% CI 0.28-0.59) after adjusting for multiple risk factors. Similarly, the discharge prescription of either an ACE-I or ARB was associated with a significant reduction in adjusted 1-year mortality (OR 0.72, 95% CI 0.58-0.91). However, among patients on dialysis, there was no benefit of ACE-I or ARB on either 30-day or 1-year mortality.

Conclusions Angiotensin-converting enzyme inhibitors and ARB are underused in patients with heart failure with chronic kidney disease. Given the reduction in 30-day and 1-year mortality, these medications should be considered in most patients with heart failure, independent of underlying renal function. Among patients on hemodialysis, further investigation is warranted. (Am Heart J 2007;153:1064-73.)

Congestive heart failure (CHF) is an increasingly prevalent condition in the United States and now affects 2.2% of the population.[1] There is strong evidence indicating that the use of angiotensin-converting enzyme inhibitors (ACE-I) among patients hospitalized with CHF results in decreased mortality.[2-8] There are also data confirming angiotensin receptor blockers (ARB) can provide a similar reduction in mortality compared to ACE-I.[9-11] The data from these trials form the basis for the American College of Cardiology/American Heart Association guidelines for the management of patients with chronic heart failure.[12,13] Contemporary data suggest the use of ACE-I and ARB remains suboptimal even in patients who have no contraindications to either therapy.[14]

Renal dysfunction is an independent predictor of morbidity and mortality in the setting of CHF. The role of ACE-I and ARB in this group of patients is less well established for 2 major reasons. First, randomized clinical trials have typically excluded patients with severely impaired renal dysfunction. Second, physicians have been reluctant to initiate either medication in patients with renal impairment because of the fear of precipitating acute renal failure or hyperkalemia. Consequently, there is a knowledge gap regarding the potential benefits and risks of ACE-I in patients with CHF and associated chronic kidney disease (CKD).

The population-based Minnesota Heart Survey (MHS) is uniquely suited to address the inhospital and discharge use of CHF medical therapies. We hypothesized (1) ACE-I

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and ARB are underused in patients with CHF and coexistent CKD; (2) the inhospital use of ACE-I and ARB in patients with CHF and severe renal insufficiency is associated with a significant reduction in 30-day mortality; and (3) the discharge prescription of ACE-I and ARB in patients with CHF and severe renal insufficiency is associated with a significant reduction in 1-year mortality.

Design and methods

The MHS is an ongoing surveillance project of CHF in all hospitalized patients 35 to 84 years of age residing in the Minneapolis–St Paul metropolitan area. The patient sample is based on an *International Classification of Diseases, Ninth Revision* (*ICD-9*) discharge diagnosis of CHF. The random selection of patient records is determined by a computer, and the medical records are abstracted by trained nurses. The extensive abstraction process includes demographic details, cardiac risk factors, medical history, clinical presentation, relevant laboratory and electrocardiographic data, medications, and inhospital complications.[15]

We identified patients in the MHS database with CHF using the Framingham criteria.[16,17] Major criteria for CHF include paroxysmal nocturnal dyspnea, orthopnea, engorged jugular veins, an S3 gallop, hepatomegaly, cardiomegaly, pulmonary edema, and a weight gain ≥4.5 kg. Minor criteria include dyspnea on exertion, cough, swollen extremities, tachycardia, and pleural effusion. The Framingham definition for CHF requires either ≥2 major criteria or the combination of 1 major criterion and ≥2 minor criteria. Both patients presenting to the hospital with CHF and those subsequently diagnosed with CHF during their hospitalization were included in the analysis.

The United States Renal Data System (USRDS) maintains a database on all patients with end-stage renal disease. We obtained permission from the USRDS to merge the MHS and USRDS data to identify patients who were on dialysis before hospitalization. All personal identifiers were removed before data analysis to ensure Health Insurance Portability and Accountabilty Act (HIPAA) compliance.

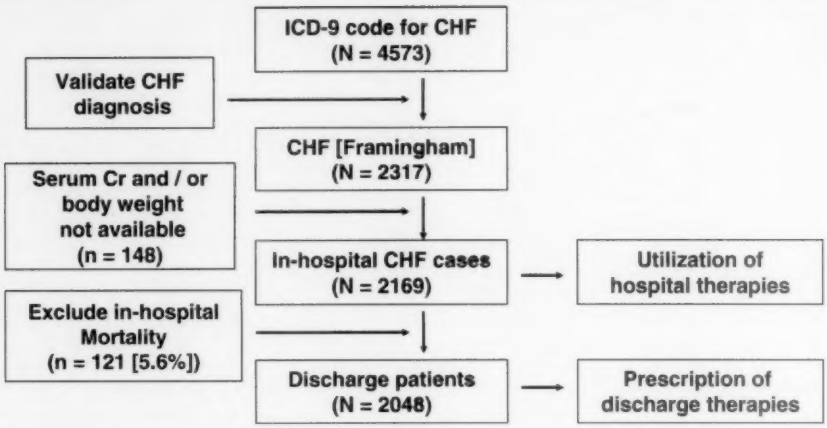
Glomerular filtration rate (GFR), a surrogate of renal function, was estimated using the Cockcroft-Gault equation. Serum creatinine was recorded at the time closest to the diagnosis of CHF. For most patients, this specimen was obtained at the time of hospital admission. A stratification scheme consistent with National Kidney Foundation Guidelines categorized renal function into 1 of 5 categories: stage 1 (≥90 mL/min), stage 2 (60-89 mL/min), stage 3 (30-59 mL/min), stage 4 (15-29 mL/min), and stage 5 (<15 mL/min).[18] Patients on dialysis before hospitalization were incorporated into the stage 5 group. Trends in characteristics across renal function strata were assessed using the Cochran-Armitage test for dichotomous variables and general linear models for continuous variables. The prescription rates—both inhospital and at discharge—of ACE-I, ARB, β-blockers, diuretics, aldosterone blockers, and loop diuretics were calculated for patients in each renal function stratum. The MHS project was able to identify whether a patient was treated with either hydralazine or a nitrate but did not obtain further detail. Characteristics associated with the use of ACE-I or ARB were assessed by logistic regression, and the individual renal function categories were forced into the model.

Mortality was measured at several time points—inhospital, 30 days, 6 months, and 1 year. All mortality data were presented after adjusting for multiple covariates. General linear models, stratified by renal function, were used to measure the association of inhospital ACE-I/ARB use with 30-day mortality and the association of discharge ACE-I/ARB use with 1-year mortality. Patients who died within 48 hours of admission were excluded from the 30-day mortality analyses because their condition may have precluded the early oral administration of either medication. Separate models were constructed to analyze GFR as both a 5-level ordinal variable and a continuous parameter. Covariables entered into the risk adjustment model included age, sex, body mass index (BMI), cardiovascular risk factors, documentation of prior coronary artery disease (angina, myocardial infarction, documented coronary atherosclerosis), prior coronary revascularization (percutaneous transluminal coronary angioplasty [PTCA], coronary artery bypass graft [CABG]), peripheral arterial disease, stroke, dementia, atrial fibrillation, use of medications in hospital and at discharge (β-blocker, hydralazine/nitrates, aldosterone blockers, and diuretics), systolic blood pressure (BP) and pulse at the time of diagnosis, serum potassium, ejection fraction (EF), inotropic agents, intraaortic balloon pump, and coronary revascularization (PTCA, CABG) during the index hospitalization. Ejection fraction data were abstracted both qualitatively and quantitatively where available and were dichotomized using an EF of 35% as a cut point. The selection of variables was based on clinical experience and known predictors of mortality. An interaction term was entered into both the 30-day and 1-year models to assess whether the potential benefit of ACE-I/ARB differed across varying levels of renal function. The reference group was patients with preserved renal function (GFR >90 mL/min) who were not treated with an ACE-I or ARB. A propensity score was developed using the aforementioned covariates to account for factors influencing patient allocation to ACE-I or ARB. The estimates were nearly identical to the results obtained from the general linear models. Consequently, we elected to report the results from the general linear model.

We were interested in determining whether ACE-I and ARB were used more frequently among patients on hemodialysis because the target organ could not be further jeopardized. We were also interested in knowing whether these medications offered a differential benefit among patients on hemodialysis compared to those not on hemodialysis. We therefore performed a post hoc subgroup analyses on the limited number of patients with stage 5 renal dysfunction, stratifying them into 2 groups based on whether they were on dialysis before hospitalization. The prescription of ACE-I and ARB were compared between patients on hemodialysis and those not on hemodialysis. The association of inhospital ACE-I and ARB use with 30-day age- and sex-adjusted mortality and the association of discharge prescription of these medications with 1-year age- and sex-adjusted mortality were similarly assessed by tabular methods. All statistical analyses were performed using SAS (version 9.1; SAS Institute, Cary, NC).

The MHS is a National Institutes of Health–supported study, and this study was approved by the institutional review boards of the participating institutions. No other external source of funding was used for this investigation.

Figure 1



Derivation of study sample from MHS cohort of CHF patients. *International Classification of Diseases, Ninth Revision* discharge diagnosis codes were used to identify patients with CHF from the MHS. The diagnosis of CHF was validated using the Framingham criteria. Inhospital and 30-day mortality were measured using the entire cohort. The 6-month and 1-year mortality were based on the subgroup of patients who survived the index hospitalization.

Main outcome measures

The outcome measure was all-cause mortality. Using the admission date as the reference, mortality was measured at discharge, 30 days, 6 months, and 1 year. Inhospital mortality was identified directly through medical record abstraction; postdischarge mortality was supplied by MINNDEX (Minnesota Death Index, Minneapolis, MN), a software program that analyzes mortality tapes provided by the state of Minnesota.[19]

Main results

We identified 4573 patients with an *ICD-9* discharge diagnosis of CHF who were hospitalized in the Minneapolis–St Paul metropolitan area hospitals between January 1 and December 31, 2000. Figure 1 describes the derivation of the study sample. We were able to validate the diagnosis of CHF using the Framingham criteria in 2317 patients. Both a weight and serum creatinine were available in 2169 (93.6%) patients, permitting the calculation of a serum GFR. This cohort—mean age, 69.1 ± 11.0 years—constituted the inhospital population in whom the use of medical therapies was assessed. The GFR was ≥90 mL/min in 469 (21.7%), 60 to 89 mL/min in 546 (25.1%), 30 to 59 mL/min in 773 (35.6%), 15 to 29 mL/min in 238 (11.0%), and <15 mL/min in 143 (6.6%). Both clinical characteristics and hospital therapies varied by degree of renal dysfunction (Table I). Trends in characteristics were consistent from stage 1 to stage 4 kidney disease. However, patients with stage 5 kidney disease included numerous individuals on dialysis, and their characteristics were quite distinct from those with less severe renal insufficiency. Overall, patients with worsening renal function tended to be older and were more likely to be female. The prevalence of cardiac risk factors—hypertension and diabetes—increased with declining renal function, whereas the prevalence of smoking decreased. Atherosclerosis (coronary artery disease, peripheral arterial disease, and cerebrovascular disease) was also more prevalent among patients with poor renal function. The left ventricular EF (LVEF) was reduced among patients with worse renal function as well. Patients with worse renal function were less likely to undergo PTCA during their hospitalization.

The inhospital use of ACE-I declined with worsening renal function with a steep cutoff among patients who had a GFR <30 mL/min (Figure 2A). Angiotensin-converting enzyme inhibitors were administered during hospitalization to 319 patients (68.0%) with a GFR >90 mL/min and to 157 patients (42.3%) with a GFR <30 mL/min. The increased use of ARB (11.3%) in patients with worse renal function partially offset the lower use of ACE-I in this group. The use of hydralazine and/or nitrates steadily increased as renal function worsened. Renal function did not appear to have any impact on the inhospital prescription of β-blockers (Table I).

The discharge prescription of CHF therapies paralleled the inhospital use of these medications (Figure 2B). The discharge prescription rates were slightly reduced compared to the inhospital rates,

Table I. Comparison of patients with CHF, stratified by renal function

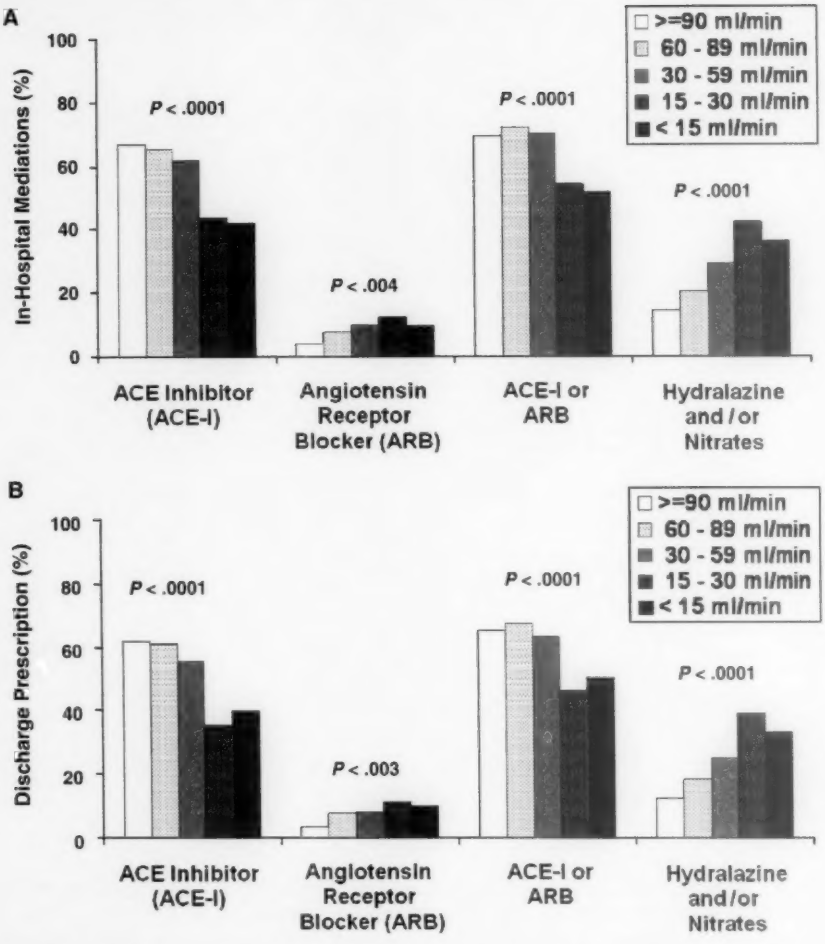
	Stage 1 (≥90 mL/min)	Stage 2 (60-89 mL/min)	Stage 3 (30-59 mL/min)	Stage 4 (15-30 mL/min)	Stage 5 (<15 mL/min)	P
N	469	546	773	238	143	
Demographics						
Age (mean ± SD)	59.8 ± 11.2	69.5 ± 9.3	73.7 ± 8.1	73.8 ± 8.8	68.0 ± 12.7	<.0001
Male (%)	63.5	55.7	48.1	42.0	49.0	<.0001
Cardiac risk factors						
Hypertension (%)	66.1	68.7	71.3	81.1	84.6	<.0001
Diabetes (%)	39.0	36.5	35.1	39.9	48.3	.25
Hypercholesterolemia (%)	39.2	41.2	39.5	34.0	35.7	.17
Tobacco use (%)	31.8	20.9	14.2	11.8	18.2	<.0001
Prior conditions						
Coronary artery disease (%)	44.1	55.9	57.6	64.3	60.8	<.0001
Prior PTCA (%)	13.7	14.5	15.5	13.0	14.7	.75
Prior CABG (%)	13.2	21.3	25.1	28.2	18.9	<.0001
Cerebrovascular disease (%)	12.4	18.9	23.4	26.1	27.3	<.0001
Peripheral arterial disease (%)	11.3	15.8	18.1	21.0	39.9	<.0001
Atrial fibrillation (%)	22.2	22.9	33.5	35.3	29.4	.0001
Dementia (%)	6.2	8.2	8.3	10.1	9.8	.06
Clinical presentation						
BMI (kg/m^2)	34.3 ± 9.0	28.8 ± 6.1	26.8 ± 5.7	25.9 ± 5.7	25.7 ± 5.4	<.0001
Systolic BP (mm Hg)	143 ± 30	140 ± 31	140 ± 35	134 ± 37	146 ± 40	.85
Pulse (beat/min)	97 ± 25	94 ± 25	93 ± 27	89 ± 23	89 ± 24	<.0001
Serum potassium (mEq/L)	4.0 ± 0.6	4.1 ± 0.6	4.3 ± 0.7	4.5 ± 0.8	4.8 ± 0.9	<.0001
K+ >4.5 (mEq/L) (%)	14.1	17.6	30.1	45.4	53.9	<.0001
Serum creatinine (mg/dL)	132 ± 43.9	74 ± 8.6	45 ± 8.4	23 ± 4.3	14 ± 12.3	<.0001
LVEF <35% (%)	33.9	35.9	42.6	45.4	34.3	.013
Inhospital therapies						
β-Blockers (%)	51.2	49.6	54.3	46.6	49.0	.77
Aldosterone blockers (%)	22.0	18.9	21.6	14.3	5.6	.0003
Hyralazine/nitrates (%)	14.7	20.4	28.7	40.3	35.0	<.0001
Diuretics (%)	97.0	97.6	97.8	97.9	58.0	<.0001
Inotropic agents (%)	9.4	10.8	16.8	20.6	16.1	<.0001
Intraaortic balloon pump (%)	3.2	1.7	1.6	0.8	1.4	.03
Coronary angioplasty (%)	6.4	5.9	3.4	2.1	2.1	.0004
Coronary bypass surgery (%)	3.6	3.7	4.0	1.7	1.4	.17

presumably due to the development of either allergic reactions or adverse side effects during hospitalization. The use of ACE-I declined with worsening renal function, whereas the use of ARB increased with worsening renal function. The combined use of ACE-I or ARB declined as well, although the greatest difference was among patients with a GFR <30 mL/min. There was no significant difference in the discharge prescription of β-blockers among patients with different renal function (data not shown).

Several characteristics were significantly associated with the prescription of ACE-I or ARB during hospitalization (Table II). Male sex, as well as the presence of hypertension, diabetes, and hypercholesterolemia, were all strongly associated with the prescription of either of these medications. In addition, coronary artery disease, LVEF <35% and prior coronary revascularization were significantly associated with the inhospital prescription of these medications. The mean serum creatinine was significantly less among patients prescribed these therapies compared to those who were not prescribed these agents. Patients prescribed ACE-I or ARB during their hospitalization were more likely to receive other standard cardiovascular therapies including β-blockers, aldosterone blockers, and diuretics. Coronary revascularization—both PTCA and CABG—were also more likely to be performed among patients receiving ACE-I or ARB.

Glomerular filtration rate was strongly associated with mortality, whether measured during hospitalization, at 30 days, at 6 months, or at 1 year (Figure 3). The fully adjusted 30-day mortality was lower among patients who received ACE-I or ARB compared to those patients who received neither therapy (Table III). There was no interaction between severity of renal dysfunction and use of ACE-I or ARB. Among the 2286 patients (98.7%) who survived the initial 48 hours of hospitalization and in whom receipt of standard medical therapies may have arguably had a greater impact, the results were essentially unchanged.

Figure 2



A, Prescription of standard medical therapies during index hospitalization, age- and sex-adjusted, and stratified by renal function. This analysis includes all patients admitted to hospital with a validated diagnosis of CHF in whom GFR could be calculated. **B**, Prescription of standard medical therapies at hospital discharge, age- and sex-adjusted, and stratified by renal function. This analysis is restricted to patients with a validated diagnosis of CHF who survived the index hospitalization and in whom GFR could be calculated.

We performed a post hoc subgroup analysis on patients (n = 143) with severe renal dysfunction (GFR <15 mL/min) and found 100 (69.9%) of these patients were on hemodialysis before hospitalization. A prior history of dialysis did not have a significant influence on the use of ACE-I or ARB, either inhospital (43.5% on dialysis vs 53.3% not on dialysis, P = nonsignificant) or at discharge (39.4% on dialysis vs 53.5% not on dialysis, P = nonsignificant). The P value interaction between inhospital use of ACE-I or ARB and dialysis on 30-day mortality was .10, and the P value for the interaction between discharge use of ACE-I or ARB and dialysis was .22. Among patients on dialysis, the use of either ACE-I or ARB was not associated with any significant reduction in mortality, either at 30 days or 1 year (Figure 4). In contrast, these medications appeared to be associated with a mortality reduction among patients not on dialysis. At 30 days, there was a 34% relative risk reduction in mortality (12.3% vs 18.5%, P = .05). At 1 year, there was a 73% relative reduction in mortality (11.1% vs 41.0%, P = .05).

Table II. Characteristics associated with the inhospital administration of ACE-I or ARB

	ACE-I or ARB administered in hospital	ACE-I or ARB not administered in hospital	P
N	1451	718	
Demographics			
Age (mean ± SD)	68.9 ± 11.2	69.7 ± 10.8	.14
Male (%)	55.0	48.3	.004
Cardiac risk factors			
Hypertension (%)	74.6	65.2	<.0001
Diabetes (%)	40.0	33.4	.004
Hypercholesterolemia (%)	42.1	32.7	<.0001
Tobacco use (%)	20.0	18.9	.54
Prior conditions			
Coronary artery disease (%)	59.2	47.1	<.0001
Prior PTCA (%)	16.3	10.9	.0007
Prior CABG (%)	24.1	16.0	<.0001
Cerebrovascular disease (%)	20.9	19.5	.45
Peripheral arterial disease (%)	17.1	19.2	.22
Atrial fibrillation (%)	27.4	30.2	.16
Dementia (%)	7.0	10.4	.005
Clinical presentation			
BMI (kg/m^2)	29.7 ± 7.0	29.3 ± 7.9	.20
Systolic BP (mm Hg)	144 ± 34	135 ± 32	<.0001
Pulse (beat/min)	93 ± 25	94 ± 27	.78
Serum potassium (mEq/L)	4.2 ± 0.7	4.2 ± 0.8	.77
K+ >4.5 (mEq/L) (%)	26.1	28.1	.30
Serum creatinine (mg/dL)	68.9 ± 42.1	62.0 ± 47.3	.0006
LVEF <35% (%)	47.0	22.1	<.0001
Inhospital therapies			
β-Blockers (%)	56.0	41.6	<.0001
Aldosterone blockers (%)	23.9	9.4	<.0001
Hyralazine/nitrates (%)	26.5	22.8	.07
Diuretics (%)	96.5	91.9	<.0001
Inotropic agents (%)	13.9	14.3	.79
Intraaortic balloon pump (%)	1.9	1.7	.67
Coronary angioplasty (%)	5.5	2.2	.0005
Coronary bypass surgery (%)	3.9	2.2	.03

Discussion

We confirmed renal dysfunction as a strong predictor of both short- and intermediate-term mortality among patients hospitalized with CHF. We documented a benefit of ACE-I and ARB on 30-day and 1-year mortality among patients with CHF, independent of the degree of severity of renal dysfunction.

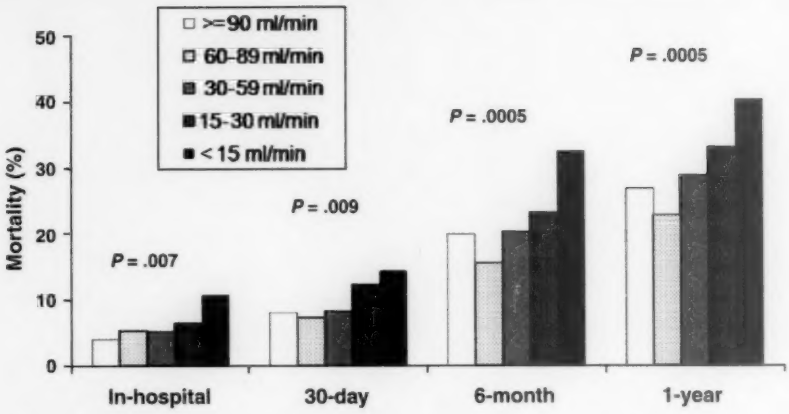
In spite of the potential benefit of these medications, we found an inverse correlation between the degree of renal dysfunction and the use of both ACE-I and ARB. Interestingly, ACE-I and ARB did not appear to have an impact on mortality among dialysis patients.

The clinical significance of our findings stems from the high prevalence of renal dysfunction among patients with CHF. McAlister et al[20] recently documented a GFR ≤ 30 mL/min in 16% of CHF patients and a GFR 30 to 59 mL/min in 40% of patients. The association of renal dysfunction and increased cardiovascular morbidity and mortality is well documented in the literature.[16,17,21-23] The existence of both conditions frequently reflects atherosclerotic burden, and so, it should not be surprising that patients with chronic renal sufficiency suffer increased mortality. In the cardiac health study, renal dysfunction was an independent predictor for the development of cardiovascular disease, CHF, and cardiovascular mortality.[23] Hillege et al,[24] in a recent analysis of the CHARM trials, found impaired renal function to be a strong predictor of death, cardiovascular mortality, and rehospitalization for CHF.

Although multiple studies have addressed the poor prognosis of CHF patients with renal dysfunction, few investigators have addressed the impact of medical therapies among these patients. Randomized clinical trials of both ACE-I have tended to exclude patients with impaired renal function, as defined by a serum Cr >2.5 mg/dL. In a recent publication, McAlister et al[20] found ACE-I had a similar benefit on mortality at 2.5 years whether the patients had a GFR ≥60 mL/min (OR 0.28 [95% CI 0.11-0.70]) or a GFR <60 mL/min (OR 0.46 [95% CI 0.26-0.82]).

The use of ACE-I among patients with severe renal insufficiency is clearly not an established practice. In our

Figure 3



Mortality for CHF patients stratified by GFR during index hospitalization. Crude mortality rates—inhospital, 30-day, 6-month, and 1-year are referenced from admission date of index hospitalization. The mortality data are fully adjusted for the covariates in the model.

Table III. Thirty-day adjusted mortality for CHF patients, stratified by inhospital prescription of ACE-I or ARB

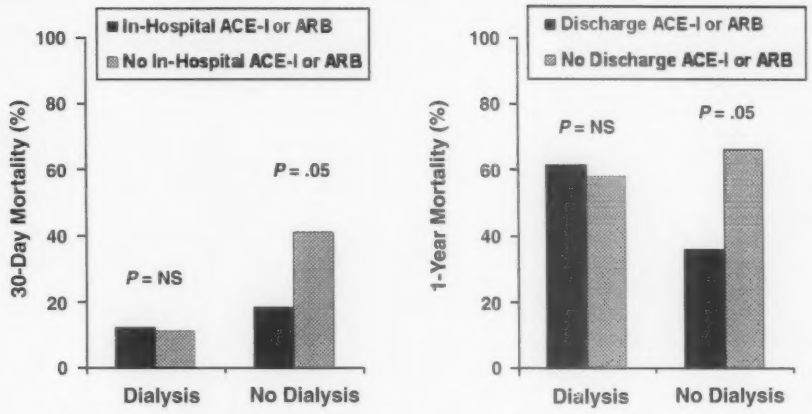
Renal function (GFR)	Stage 1 (≥90 mL/min)	Stage 2 (60-89 mL/min)	Stage 3 (30-59 mL/min)	Stage 4 (15-29 mL/min)	Stage 5 (<15 mL/min)
All CHF hospitalizations*					
n	469	546	773	238	143
ACE-I or ARB	6.1%	6.3%	5.4%	9.4%	11.9%
No ACE-I or ARB	11.3%	8.6%	14.0%	18.5%	22.8%
P	.07	.37	.0001	.008	.03
Patients surviving initial 2 d					
n	469	541	765	232	139
ACE-I or ARB	5.8%	5.8%	5.1%	8.4%	13.0%
No ACE-I or ARB	11.1%	6.0%	11.8%	15.8%	20.6%
P	.05	.91	.001	.03	.13

* The analysis was performed for all patients admitted with CHF and the subgroup of patients who survived the initial 2 days of hospitalization. The *P* value for interaction between trend in use of medication and severity of renal disease was .32 for the entire cohort and .33 for patients surviving the initial 2 days of hospitalization.

study, approximately 50% of patients with a GFR <30 mL/min received either an ACE-I or ARB. Bakris and Weir[25] recently reviewed 12 randomized clinical trials of ACE-I in patients with baseline renal insufficiency (serum Cr >1.4 mg/dL). They found a strong association between acute increases in serum creatinine that stabilized within the first 2 months of ACE-I therapy and long-term preservation of renal function. The authors concluded ACE-I should only be withheld when the rise in creatinine exceeds 30% above baseline within the first 2 months of ACE-I initiation or hyperkalemia (serum potassium ≥5.6 mmol/L) develops. Philbin et al[26] studied 1076 hospital survivors identified from a consecutive series of CHF inpatients and found angiotensin-converting enzyme inhibitors were associated with a clinical benefit among patients with a serum Cr ≤1.9 mg/dL. Among patients with a serum Cr ≥2.0 mg/dL, there was no impact on mortality, rehospitalization, or quality of life. In a recently published randomized clinical trial of 224 nondiabetic patients with advanced renal insufficiency (serum Cr 3.1-5.0 mg/dL), Hou et al[27] found benazepril reduced both the level or proteinuria and the rate of decline in renal function.

The absence of a significant mortality benefit of ACE-I and ARB among dialysis patients is an interesting observation and, to the best of our knowledge, has not been previously reported. McCullough et al[28] found a benefit of ACE-I among patients with end-stage renal disease who were hospitalized in the coronary care unit with either an acute coronary syndrome or CHF. After

Figure 4



Association of inhospital use of ACE-I and/or ARB with 30-day and 1-year adjusted mortality. The association of inhospital ACE-I and/or ARB prescription with 30-day and 1-year adjusted mortality is stratified by prior exposure to hemodialysis.

adjusting for confounders, there was a 37% reduction in all-cause mortality among patients who received ACE-I ($P = .014$). In contrast, we found no benefit of ACE-I or ARB among patients with a GFR <15 mL/min who were on dialysis. Interestingly, we observed a 34% relative reduction in 30-day mortality and a 73% reduction in 1-year mortality among patients with a GFR <15 mL/min who were not on dialysis. The benefit of these agents among stage 5 nondialysis patients must be interpreted with caution due to the small sample size.

Congestive heart failure is a prevalent finding among dialysis patients and accounts for significant morbidity and mortality in this population.[29-31] The pathologic characteristics of dilated cardiomyopathy in dialysis patients—interstitial fibrosis and severe myocyte hypertrophy—are postulated to contribute to the dismal clinical prognosis.[32] These findings may explain why ACE-I and ARB may not achieve the same outcomes in patients with dialysis. Alternatively, the failure of these medications to provide a benefit may stem from the fact that the kidney is both intrinsically involved in the metabolism of the drug and serves as the target organ for these agents. Finally, our inability to identify a benefit may stem from selection bias or the relatively small number of patients with CHF and coexistent hemodialysis.

It should not be surprising that the CHF guidelines have been unable to achieve a consensus regarding the use of ACE-I/ARB in patients with severe renal dysfunction.[12,33,34] Most of the randomized clinical trials used serum Cr rather than estimated GFR and excluded patients with impaired renal function (serum Cr >2.0 mg/dL). In the studies that did permit a serum Cr as high as 3.0 mg/dL, few patients with severe renal dysfunction were actually enrolled. There is evidence from the CONSENSUS trial to support the use of ACE-I in patients with moderate renal insufficiency (GFR 30-60 mL/min). In the recently published American College of Cardiology/American Heart Association guidelines, GFR is not used to stratify risk.[12] The guidelines indicate ACE-I should be used with caution among patients with markedly increased levels of serum creatinine (>3 mg/dL).

Recent data from the ADHERE registry indicates ACE-I and ARB are underused among patients with CHF and coexistent renal dysfunction. The collaborators identified renal insufficiency (Cr ≥2.0 mg/dL) among 11798 (20.0%) of 58919 admissions of acute decompensated heart failure. Thirty-five percent of these patients were on an ACE-I before admission and 14% were on an ARB. An additional 9% of patients had an ACE-I added to their regimen at discharge, and 3% of patients had an ARB added to their regimen. These data emphasize the importance of reevaluating patients with CHF to determine whether they are appropriate candidates for ACE-I and/or an ARB.

Several factors presumably explain the reduced use of ACE-I among CHF patients with pre-existing CKD. First, ACE-I have the potential to precipitate hyperkalemia and increase the toxicity of other agents (ie, digoxin) in the setting of CKD.[26,33] Second, a significant increase in serum creatinine (>0.3 mg/dL) with the use of ACE-I is observed in 15% to 30% of CHF patients.[34] This is of greatest concern among patients with renal artery stenosis in whom the institution of an ACE-I may reduce GFR by reducing the efferent arteriolar pressure.[35]

Finally, patients with CHF secondary to systolic dysfunction frequently have reduced systolic BP, and physicians often struggle with balancing the benefits of multiagent therapy against the adverse effects associated with systemic hypertension.

There were several limitations to our analysis. First, this was a retrospective study and was subject to both diagnosis misclassification as well as selection bias. We chose the Framingham definition of CHF to validate the *ICD-9* diagnosis of CHF. To address the issue of selection bias, we developed risk adjustment models and included covariates associated with CHF and worse prognosis. Second, the MHS project is cross-sectional, sampling each patient at the time of hospitalization for CHF, and does not collect information post discharge other than death because of privacy regulations. Consequently, it is difficult to estimate patient compliance with long-term ACE-I and/or ARB use as well as which patients with CKD may have gone on to require hemodialysis post discharge. Third, as with any retrospective analysis, there may have been unmeasurable variables (eg, microalbuminuria) and unknown confounders that modified the association between the use of ACE-I/ARB and mortality. The incorporation of a propensity model had minimal impact on the estimates. Finally, there may have been a small number of Minnesota residents who moved during the year after hospital discharge for whom we could not identify long-term mortality.

Conclusions

Chronic kidney disease is highly prevalent among CHF patients, and the severity of CKD is a strong predictor of short- and intermediate-term mortality. Although ACE-I and ARB are not widely used in this population, our data suggests their administration may be associated with an improved survival, both at 30 days and 1 year. The initiation of these agents at low dose with careful monitoring of renal function and serum electrolytes should be considered in all patients with CHF, independent of renal function. The use of these agents in patients on hemodialysis clearly warrants further investigation.

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Relation of sex to morbidity and mortality in patients with heart failure and reduced or preserved left ventricular ejection fraction

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Background Previous studies indicate a survival advantage for women over men with chronic heart failure associated with reduced or preserved ejection fraction. Whether women with chronic heart failure are at less risk for hospitalization for worsening heart failure has not been well investigated.

Methods Using data from the DIG trial, the relationship between sex and adverse outcomes, especially the risk of hospitalization for various causes, was evaluated in patients with reduced or preserved left ventricular ejection fraction.

Results Survival was worse for men than women with either reduced (HR 1.48, 95% CI 1.33-1.65, $P < .001$) or preserved ejection fraction (HR 1.60, 95% CI 1.20-2.13, $P = .001$), with $P = .406$ for sex interaction. In contrast, the risk of hospitalization for heart failure was greater in men than women when ejection fraction was reduced (HR 1.19, 95% CI 1.07-1.33, $P = .001$) but not preserved (HR 0.90, 95% CI 0.67-1.22, $P = .494$), with $P = .003$ for sex interaction. The relative risk of hospitalization for worsening failure between reduced and preserved ejection fraction was greater in men than women (HR 5.97, 95% CI 1.40-25.56, $P = .001$ in men vs HR 2.65, 95% CI 0.68-10.31, $P = .159$ in women).

Conclusion A survival advantage for women was seen in heart failure with reduced or preserved ejection fraction. In contrast, women appeared to be at lower risk for hospitalization for heart failure only when left ventricular systolic dysfunction was present. (Am Heart J 2007;153:1074-80.)

Our group and other investigators have demonstrated that female sex is associated with improved survival in patients with heart failure due to left ventricular systolic dysfunction.[1-6] In addition, recent analyses suggest better survival for women than men when heart failure is associated with preserved left ventricular ejection fraction.[7,8] Better survival in women with heart failure raises the possibility that female sex might be associated with less morbidity as well. However, the relationship between sex and the likelihood of hospitalization for worsening heart failure has not been well investigated. Because patients survive longer with heart failure, interest has grown in understanding factors that influence the frequency of hospitalization for this syndrome. Recent studies indicate admission for decompensation is frequent not only in patients with systolic dysfunction but also preserved left ventricular ejection fraction.[9,10] Understanding the relationship of sex to the risk of hospitalization in patients with preserved systolic function is of particular interest because women predominate in this type of heart failure.[10]

To investigate the association of sex with the risk of adverse events, especially hospitalization for heart failure, a retrospective analysis of outcomes of women and men in the DIG trial was conducted.[11] The study design affords a unique opportunity to evaluate the association between sex and the risk of mortality and hospitalization, not only for worsening heart failure but other causes, across the clinical syndrome of heart failure. Data on adverse events were available not only in patients with reduced but also preserved ejection fraction who were recruited and followed by the same group of investigators using a similar study protocol and common end points.

Methods

Patients and study design

This study was based on a retrospective analysis of patients enrolled in the DIG trial.[11] Primary study outcomes were all-

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Table I. Baseline clinical characteristics by type of heart failure and sex

Characteristic	LVD Female (n = 1517)	LVD Male (n = 5273)	PEF Female (n = 407)	PEF Male (n = 581)	*P* (PEF vs LVD)	*P* (M vs F LVD)	*P* (M vs F PEF)
Age (y)	65 ± 12	63 ± 11	69 ± 11	66 ± 9.7	<.001	<.001	<.001
Race (% nonwhite)	19	13	16	12	.584	<.001	.048
Ischemic etiology (%)	62	73	49	62	<.001	<.001	<.001
Hypertension (%)	54	43	66	55	<.001	<.001	.001
Diabetes (%)	34	27	34	25	.777	<.001	.002
SBP (mm Hg)	128 ± 21	125 ± 20	140 ± 23	136 ± 20	<.001	<.001	.001
LVEF (U)	30 ± 8.9	28 ± 8.8	57 ± 8.5	54 ± 7.6	<.001	<.001	<.001
CT ratio	0.56 ± 0.08	0.52 ± 0.07	0.54 ± 0.09	0.50 ± 0.07	<.001	<.001	<.001
NYHA class	2.3 ± 0.7	2.2 ± 0.7	2.1 ± 0.7	2.0 ± 0.7	<.001	<.001	<.001
CHF score (U)	12 ± 5.1	11 ± 5.5	12.1 ± 4.7	11 ± 5.0	.224	<.001	<.001
eGFR (mL/min per 1.73m^2)	59 ± 20	65 ± 19	56 ± 20	66 ± 20	.005	<.001	<.001
Body mass index (m^2)	27 ± 6.4	27 ± 4.8	29 ± 7.7	28 ± 4.9	<.001	.600	.026

Values are shown as mean ± SD or percentage, as appropriate. *CT*, Cardiothoracic; *CHF*, congestive heart failure; *eGFR*, estimated glomerular filtration rate; *LVD*, left ventricular dysfunction; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *PEF*, preserved ejection fraction; *SBP*, systolic blood pressure.

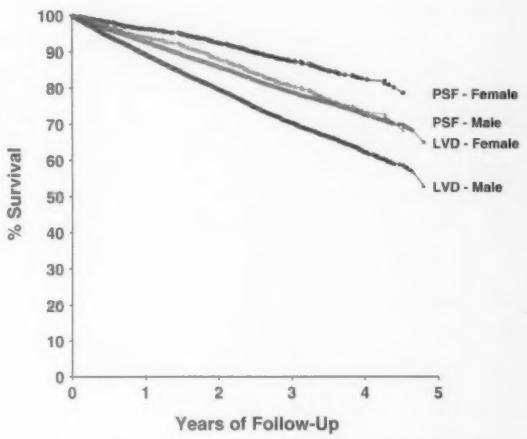
cause mortality and hospitalization for worsening heart failure, and secondary end points included all-cause hospitalization and cardiovascular hospitalization.

Statistical analysis

The principal statistical analysis of the study evaluated sex as an independent predictor of survival or risk of hospitalization for worsening heart failure in all patients and in both preserved and reduced ejection fraction patient groups. Secondary analyses considered the risk of other hospitalization end points and the risk of study outcomes by sex in subgroups based on age and investigator-assessed etiology of heart failure (ischemic versus nonischemic). For the end points, which included both death and hospitalization, deceased patients were censored at the hospitalization date if they died after experiencing a hospitalization.

To account for characteristics that may have confounded the association between sex and adverse outcomes, the following variables were tested with respect to their relationship to survival and the risk of various types of hospitalization, both in the overall population and then separately in patients with reduced or preserved ejection fraction: age, race, prior myocardial infarction, current angina pectoris, history of hypertension, etiology of heart failure (ischemic or nonischemic), estimated glomerular filtration rate, cardiothoracic ratio, New York Heart Association functional class, body mass index, symptom score, duration of heart failure, diabetes, heart rate, systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction, angiotensin-converting enzyme inhibitor, nitrate, diuretic, and vasodilator use at baseline. These variables were considered as candidates for multivariable prognostic models of end points of interest in backward-selection multivariable Cox proportional hazards modeling in all patients and both ejection fraction groups, where randomization to treatment with digoxin (yes/no) and previous digoxin use (yes/no) were included in each model to reflect the trial design. Subgroup analyses of the relationship between sex and adverse outcomes were also performed, according to etiology (ischemic and nonischemic) and age (for age ranges <60, 60-69, and ≥70 years). Adjusted Kaplan-Meier curves were constructed based on the final Cox regression models, where each covariate was taken at its mean value in the corresponding sample. Kaplan-Meier estimates of the end points at 1 year of follow-up are also reported. Comparisons of key baseline characteristics by sex and ejection fraction group were performed using standard methods (ie, Pearson χ^2 test and 2-sample *t* tests). Data are shown as mean ± SD or percentage, as appropriate.

Figure 1



Adjusted survival curves based on sex and the type of heart failure present (reduced left ventricular ejection fraction or preserved left ventricular ejection fraction).

Study population

The study population for this analysis consisted of 7778 of the 7788 patients enrolled in the trial; 10 were removed on the basis of having estimated glomerular filtration rates exceeding

Table II. Relative risk of men versus women for study end points by type of heart failure

Patient population	Mortality	Risk of hospitalization for worsening heart failure	Risk of cardiovascular hospitalization	Risk of all-cause hospitalization	Combined end point
Overall	1.47 (1.33-1.63) $P < .001$	1.17 (1.06-1.29) $P = .002$	1.12 (1.04-1.21) $P = .004$	1.18 (1.11-1.27) $P < .001$	1.31 (1.20-1.42) $P < .001$
LVD	1.48 (1.33-1.65) $P < .001$	1.19 (1.07-1.33) $P = .001$	1.15 (1.06-1.25) $P = .001$	1.19 (1.11-1.29) $P < .001$	1.33 (1.22-1.45) $P < .001$
PEF	1.60 (1.20-2.13) $P = .001$	0.90 (0.67-1.22) $P = .494$	0.93 (0.77-1.14) $P = .496$	1.14 (0.96-1.34) $P = .133$	1.20 (0.95-1.50) $P = .126$
P (interaction effect of sex by type of heart failure present)	.371	.003	.015	.498	.011

Data are presented as relative risk (95% CI). Results reflect multivariable adjustment for clinical characteristics, as listed in the Methods section.

150 mL/min per 1.73 m^2. Mean follow-up for both groups of patients was 2.9 ± 1.2 years, and data on vital status were available for 99% of the patients enrolled.

Results

Baseline characteristics

The clinical characteristics of the 7778 patients in the analysis are compared by sex and left ventricular ejection fraction group in Table I. Female sex was significantly more common in patients with preserved compared to reduced ejection fraction (41% vs 22%, $P < .001$). In both ejection fraction groups, women were significantly older, more likely to have a history of hypertension and diabetes, and less likely to have heart failure due to an ischemic etiology.

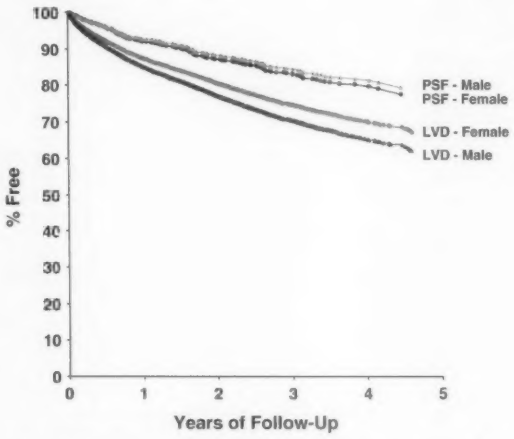
Study outcomes

In the overall study population, the 1-year mortality was 10.8%, and the 1-year risk of hospitalization for worsening heart failure was 15.9%. The risk of death and hospitalization for worsening heart failure were significantly greater in patients with reduced compared to preserved ejection fraction (adjusted $P = .016$ and $P < .001$, respectively).

Sex and adverse outcomes

Multivariable modeling demonstrated better survival in women compared to men (Figure 1, Table II). In contrast, the influence of sex on the risk of hospitalization for heart failure varied by the type of heart failure present. In patients with reduced ejection fraction, female sex was associated with a lower risk of hospitalization for worsening heart failure (adjusted relative risk of men vs women was 1.19, 95% CI 1.07-1.33, $P = .001$) (Figure 1, Table II). However, there was no significant association between sex and the risk of hospitalization for worsening heart failure in patients with preserved ejection fraction (adjusted relative risk of men versus women was 0.90, with 95% CI 0.67-1.22, $P = .494$) (Figure 2, Table II), with $P = .003$ for interaction of effect of sex on outcomes based on type of heart failure present. The risk of hospitalization for worsening heart failure was significantly greater in all patients with reduced versus preserved left ventricular ejection fraction (adjusted relative risk of 5.48, with 95% CI 2.10-14.31, $P < .001$). This difference in relative risk of hospitalization for worsening heart failure between reduced and preserved ejection fraction was greater in men than women (adjusted relative risk 5.97, 95% CI 1.40-25.56, $P = .016$ in men vs 2.65, 95% CI 0.68-10.31, $P = .159$ in women). Findings concerning the likelihood of cardiovascular hospitalization were similar with regard to sex. Cardiovascular hospitalization was more likely in men than women when ejection

Figure 2



Adjusted curves showing the risk of hospitalization for worsening heart failure based on sex and the type of heart failure present (reduced left ventricular ejection fraction and preserved left ventricular ejection fraction).

fraction was reduced but not when preserved (Table II) ($P = .015$ for interaction between sex effect and type of heart failure). In contrast, men were more likely to be hospitalized for any cause in the entire study population. The point estimate of relative risk for men versus women for all-cause hospitalization was similar in preserved and reduced ejection fraction groups, and the test for interaction between sex effect and type of heart failure present was negative for this end point ($P = .462$, Table II).

There was no evidence in the overall study population that the survival advantage of women over men diminished as age advanced ($P = .116$ for interaction of age with sex effect). Likewise, the relationship between sex and the risk of hospitalization for worsening heart failure was not influenced by age in patients with reduced ($P = .492$ for interaction) or preserved ejection fraction ($P = .206$ for interaction). Whether heart failure was ascribed to ischemic or nonischemic causes, as assigned by the study investigators, was not a predictor of mortality in the overall study population (relative risk of ischemic vs nonischemic was 0.96, with 95% CI 0.88-1.05, $P = .361$) or among patients with reduced (relative risk of ischemic vs nonischemic 0.97, with 95% CI 0.88-1.06, $P = .485$) or preserved ejection fraction (relative risk ischemic vs nonischemic 0.93, with 95% CI 0.71-1.22, $P = .611$). In addition, in an all-patient analysis, the strength of the association of sex with mortality was not influenced by the cause of heart failure ($P = .829$ for interaction). Stratified analyses of all patients by etiology group also revealed a similar increase in risk for men with ischemic etiology (adjusted relative risk of men vs women was 1.49, with 95% CI 1.32-1.68, $P < .0001$) and nonischemic etiology (adjusted relative risk of men vs women was 1.46, with 95% CI 1.24-1.71, $P < .0001$). Etiology also did not influence the association between sex and risk when the type of heart failure was considered. The adjusted relative risk of men vs women was similar in patients whose etiology was ischemic or nonischemic when heart failure was due to either reduced ejection fraction (relative risk 1.49 compared to 1.47, respectively, $P = .921$ for interaction) or preserved ejection fraction (relative risk 1.57 compared to 1.66 respectively, $P = .844$ for interaction).

Discussion

The major new findings of clinical importance in our study concern the association of sex with hospitalization in patients with chronic congestive heart failure. We found that women were less likely to be hospitalized for worsening heart failure than men in the overall study population. Because clinical characteristics (including the frequency of women) and pathophysiology differ between heart failure with reduced and preserved ejection fraction, we further analyzed the association between sex and risk of hospitalization separately in these subgroups. This subgroup analysis suggested that the association between sex and risk of hospitalization for heart failure depended upon the type of left ventricular dysfunction present. Admission for decompensated heart failure was less common in women with reduced ejection fraction but was similar between men and women with preserved ejection fraction. Results available from the DIG trial also allowed assessment of the relative risk of men and women for all-cause and cardiovascular hospitalization. These other hospitalization end points showed similar increased risk for men versus women when ejection fraction was reduced. In contrast, men were not at increased risk for cardiovascular or all-cause hospitalization in patients with preserved ejection fraction, again highlighting the specific nature of the sex difference in hospitalization risk we observed. Our analysis provides additional data supporting a survival advantage for women in heart failure with reduced ejection fraction, a reduction in risk originally reported by our group and seen by others in different databases.[1-6]

Origin of sex differences

The pathophysiological mechanisms accounting for the relationship of sex to morbidity and mortality in patients with heart failure and preserved ejection fraction remain to be determined. If our data are correct, mechanistic theories must explain why improved survival in women with preserved ejection fraction is not accompanied by a similar reduction in their risk for hospitalization. Part of the difficulty in understanding sex differences in outcome in patients with heart failure and preserved ejection fraction arises from our poor general understanding of the pathophysiology of this syndrome. Mechanistic reasons to explain not only the occurrence of hospitalization for heart failure but also death are incomplete, and animal models to provide pathophysiological insights into this syndrome are only now being developed. Nevertheless, some initial hypotheses concerning the origin of sex differences may be proposed based on studies of remodeling in clinical and experimental models of hypertension and patients with aortic stenosis, conditions with pathophysiologies that may be analogous to patients with heart failure and preserved ejection fraction. These studies demonstrate a more favorable pattern of ventricular adaptation with less ventricular dilatation in women as opposed to men.[12-15] Progressive ventricular dilatation is likely to be a risk factor in heart failure due either to preserved or reduced ejection fraction. In contrast, this pattern of remodeling in women could be associated with more severe abnormalities of diastolic function or women may be more likely to retain sodium, both factors that might predispose to hospitalization but not mortality.[16] Clearly, further studies are needed to better define the

pathophysiology and role of sex in heart failure with preserved ejection fraction.

Previous experimental work has identified several potential mechanisms to explain the survival advantage of women in heart failure due to reduced ejection fraction. In states of left ventricular dysfunction, the ventricle is more dilated, and there is a greater increase in ventricular mass and more impairment of systolic function in men than women.[6,17,18] Hormonal differences have long been suspected to underlie the physiological and clinical differences in women and men with heart failure. Recent experimental work suggests that estrogen receptor β mediates the sex difference in hypertrophic response to pressure overload.[19] Interestingly, we found no evidence that the differences in outcomes between men and women varied with age, which might be expected if hormonal differences were important. However, the effects of sex-related hormones, including estrogen, on the heart are complex and the regulatory network is rich. Much additional work is needed before the role of these sex-specific hormones in outcome differences between men and women in heart failure can be clarified.[20]

Previous work

Of interest, our findings concerning sex and hospitalization differ from several prior studies.[21-27] Most other published studies have observed similar rates of hospitalization for worsening heart failure in men and women. However, several important differences between patient populations in previous work and our study may help explain these disparate results. Previous studies were based almost exclusively on the follow-up of patients hospitalized for heart failure rather than in a population of outpatients with chronic heart failure, as we investigated. Patients hospitalized for heart failure appear to be a distinct clinical subgroup with a different natural history and potentially a different pathophysiology than patients with chronic heart failure. Whether our findings related to sex and the risk of hospitalization apply to this important subset requires further investigation in larger numbers of patients.[28] The characterization of patients and follow-up in our study also differ from previous work. Prior studies often lacked documentation of systolic function, and thus, almost no studies were able to examine the relative risk of hospitalization for heart failure between men and women taking into account whether ejection fraction was reduced or preserved.[29] Our study had a much larger sample size, longer follow-up, and generally many more events than previous work, which may have allowed differences between women and men to emerge.

We are aware of 2 other recent studies that have results concerning sex differences in risk of hospitalization in outpatients with heart failure relevant to our study, one limited to patients with reduced systolic function and the other using a subset of the DIG trial patients with preserved systolic function.[22,30] The findings of Majahalme et al[22] in patients with reduced systolic function showed an increased risk of hospitalization for heart failure for women compared to men. Several aspects of their analyses may account for these discrepant findings. First, their analysis did not include adjustment for several variables that may have been significant predictors of hospital risk, including diabetes mellitus, renal function, age, and degree of left ventricular dysfunction. These characteristics relate to risk of hospitalization and appeared to differ between men and women in the ValHeFT study. We encountered a number of sex differences between women and men, and our unadjusted findings differed from our more definitive multivariable analysis. We used time to first event in our modeling, which accounts for the potential confounding of hospitalization risk because of longer survival in women. The analysis of Deswal and Bozkurt[30] examined results from the DIG trial as we did. Their reported analysis was restricted to a subset of patients enrolled in the preserved ejection fraction arm of the trial. Their findings in this subgroup of patients (719 of the 988 enrolled patients who had an ejection fraction ≥50%) were consistent with our results in all study patients with preserved ejection fraction.

Although prior results have suggested that women had lower mortality than men only when the cause of heart failure was nonischemic, the survival advantage of women in the present study did not depend on the etiology of heart failure.[1,3] However, in the DIG trial, the etiology of heart failure was determined by the investigator using data available in the context of large simple clinical trial format, and the frequency of angiographic documentation of coronary artery disease is unknown. In other studies where etiology was more carefully defined, the cause of heart failure has been associated with mortality risk in the overall population as well as influencing the relationship of sex to survival. In the DIG trial, etiology (ischemic vs nonischemic) neither predicted survival nor did it influence the association of sex with mortality. These considerations raise the possibility that the etiology of some patients may have been misclassified, thus preventing detection of these associations.[31] Ischemic etiology can be underestimated by clinical assessment alone, especially in the elderly and in diabetics,[32] characteristics that are associated with female sex.

Study limitations

Some potential limitations of our analyses of the DIG trial need to be considered. Hospitalizations were classified by the investigators; there was no independent

events committee to assign their cause. Our patient sample was recruited from outpatient clinics into a randomized clinical trial. Clinical trial patients generally are not fully representative of patients with heart failure, so our results may not be fully generalizable to all patients with chronic heart failure.

Study implications

Hospitalization for worsening heart failure is an increasingly important end point in congestive heart failure as survival has improved due to the application of evidence-based therapies. Understanding factors associated with the risk of hospitalization is important to identify potential pathophysiological mechanisms and to estimate the burden of heart failure in various patient groups. As the population ages and heart failure with preserved ejection fraction increases in frequency, our results suggest the burden of this syndrome in women will be substantial.

Conclusions

Our retrospective analysis of all patients participating in the DIG trial demonstrated women had reduced risk for mortality and hospitalization for worsening heart failure, compared to men. The survival advantage for women was seen in heart failure due to reduced or preserved ejection fraction. In contrast, the association of sex with the risk of hospitalization for worsening heart failure appeared to depend upon the degree of ventricular dysfunction present. Heart failure with preserved ejection fraction was not only more common in women but appeared to be associated with similar morbidity compared to men.

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Relation of early improvement in coronary flow reserve to late recovery of left ventricular function after β-blocker therapy in patients with idiopathic dilated cardiomyopathy

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Background β-Blocker therapy reverses left ventricular (LV) remodeling in patients with idiopathic dilated cardiomyopathy (IDC). Improvement in coronary circulation by β-blocker could play a role in these circumstances. This study investigated the relationship between change in coronary flow reserve (CFR), as a marker of coronary circulation, and subsequent improvement in LV ejection fraction (LVEF) at follow-up during carvedilol therapy in patients with IDC.

Methods Eighteen patients with IDC underwent CFR measurements by transthoracic Doppler echocardiography at baseline and after 1 month of treatment with carvedilol. A follow-up echocardiographic assessment of LVEF was done at 12 ± 6 months of treatment. The patients were classified by the degree of improvement in LVEF in the follow-up study, as group A (LVEF change ≥10%) and group B (LVEF change <10%).

Results Although there was no significant difference in CFR between the 2 groups at baseline, CFR was significantly higher in group A than in group B at 1 month of therapy (3.7 ± 0.5 vs 2.5 ± 0.9; $P < .01$). Coronary flow reserve change after 1 month was significantly greater in group A than in group B (1.3 ± 0.6 vs 0.4 ± 0.5; $P < .01$). Logistic regression analysis revealed that CFR change predicted a significant improvement in LVEF at follow-up ($P < .05$). Furthermore, a significant correlation was found between the change in CFR after 1 month and that in LVEF on follow-up ($r = .65$, $P < .01$).

Conclusions This study demonstrated that early change in CFR is associated with subsequent improvement in LVEF, suggesting the potential predictive value of coronary circulation for subsequent LV reverse remodeling after β-blocker therapy in patients with IDC. (Am Heart J 2007;153:1080.e1-1080.e6.)

Coronary endothelial dysfunction and hyperlipidemia are independently associated with diastolic dysfunction in humans

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Background Coronary endothelial dysfunction (CED) and DHF are both associated with myocardial ischemia and CAD risk factors. The objective of the this study was to determine if CED and CAD factors are associated with diastolic dysfunction before the development of occlusive CAD or clinical heart failure.

Methods Patients with normal ejection fraction and nonocclusive CAD who underwent coronary endothelial function studies were identified. Left ventricular relaxation was assessed by tissue Doppler assessment of early diastolic ascent of the septal mitral annulus (Ea). Multiple linear regression was used to investigate whether coronary risk factors influenced diastolic function after adjusting for the presence of CED.

Results A total of 160 patients had adequate assessment of diastolic relaxation. With multiple linear regression models, %ΔCBF ($P = .018$) was associated with a higher Ea; in contrast, older age ($P < .001$), female sex ($P = .028$), higher left ventricular mass index ($P = .016$), and higher nonhigh-density lipoprotein cholesterol ($P = .022$) were associated with a lower Ea.

Conclusion Coronary endothelial dysfunction and hyperlipidemia are independently associated with impaired relaxation in patients with normal ejection fraction in the absence of occlusive CAD and heart failure. The current study suggests a new potential mechanism for the development of endothelial and diastolic dysfunction in humans. (Am Heart J 2007;153:1081-7.)

Heart failure is a major cause of morbidity and mortality.[1] Heart failure with preserved ejection fraction also known as DHF accounts for more than 50% of heart failure cases[2] and plays a central role in the etiology and progression of heart failure.[3-6] Coronary endothelial dysfunction (CED) has been implicated in the pathogenesis of diastolic dysfunction in experimental models,[7-9] but their association in humans remain unclear.

Coronary atherosclerosis risk factors are associated with endothelial dysfunction[10] and subsequent development of CAD. Significant CAD has long been known to be associated with elevated left ventricular diastolic pressures.[11] Epidemiologic studies have shown that coronary atherosclerosis risk factors are common in people with diastolic dysfunction[6,12] and in those with DHF.[2,13-16] Thus, coronary atherosclerosis risk factors may play a key role in the pathogenesis of diastolic dysfunction and DHF by promoting CED and CAD. Indeed, a recent study suggested that statins, potent modulators of endothelial function, improved mortality in patients with DHF.[17] These investigators speculated that statins may affect a variety of lipid related and independent factors, which could modulate diastolic function. However, little is known of the potential effects of hyperlipidemia on diastolic function.

The objective of the current study was to determine if coronary atherosclerosis risk factors and endothelial dysfunction are associated with diastolic dysfunction before the development of occlusive CAD or clinical heart failure. Thus, we retrospectively looked at the association between coronary risk factors and coronary endothelial function in humans with no significant

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CAD who had preserved ejection fraction and no heart failure symptoms.

Methods

Patient population and design

The present study was approved by the Mayo Clinic institutional review board and all subjects had given their consent. This study was a retrospective analysis of all patients referred to the Mayo Clinic between January 1999 and November 2005 for cardiac catheterization who underwent coronary endothelial function assessment and entered into a registry. Patients without significant epicardial coronary stenoses (no stenosis >30% diameter) who had also had an echocardiogram during their index evaluation were eligible for the present study. Exclusion criteria were the presence of congestive heart failure symptoms as assessed by the primary referring cardiologist, an ejection fraction <50%, valvular heart disease (defined as any regurgitation or stenosis of at least moderate degree), pericardial disease, and congenital heart disease.

Evaluation of coronary risk factors

Hyperlipidemia was defined as specified by the 2001 National Cholesterol Education Program report.[18] The body mass index (BMI) was calculated by dividing the patient's weight in kilograms by the square of the patient's height in meters. Patients were considered hypertensive if their blood pressure was ≥140/90 mm Hg, or if they were being treated with antihypertensive medications. Current smokers were tobacco smokers within last 6 months, previous smokers were smokers who quit more than 6 months ago, and never smokers were patients who never smoked.

A highly sensitive latex-particle-enhanced immunoturbidimetric assay (Kamiya Biomedical, Seattle, Wash) was used to quantitate the level of C-reactive protein (CRP).

Fasting blood samples for complete blood count, creatinine, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and glucose, were drawn at the time of coronary angiography. These assays were performed by using standard laboratory techniques according to established methodology.

Assessment of coronary vasoreactivity

Diagnostic coronary angiography was performed, as described elsewhere.[19] Cardiac medications were withheld for 48 hours before the study. Coronary vascular reactivity responses were studied subsequently, as previously reported.[19,20] In brief, a 0.014-in Doppler-tipped guidewire (Volcano, Santa Ana, CA) was introduced within a 2.2F coronary infusion catheter (Ultrafuse, SciMed Life System, Minneapolis, MN) into the left anterior descending coronary artery. Assessment of CFR was determined by intracoronary adenosine boluses (18-48 μg) until maximal hyperemia was achieved.[19] After allowing CBF to return to baseline, selective intracoronary infusion of incremental doses of the-endothelial dependent vasodilator, acetylcholine, was performed to the maximum tolerable dose (10^{-6}, 10^{-5}, and 10^{-4} mol/L at 1 mL/min for 3 minutes), followed by intracoronary administration of 200 μg nitroglycerin. Selective angiography was performed after each dose of acetylcholine and nitroglycerin.

Coronary artery diameter was measured by quantitative coronary angiographic analysis by an independent investigator, 5 mm distal to the tip of the Doppler wire. Coronary blood flow was calculated as previously described.[19,21] Endothelial-dependent changes in CBF were calculated by using the following equation: [(CBF after intracoronary acetylcholine − resting CBF) / resting CBF × 100 (%)] (%ΔCBF). According to previous studies linking the presence of CED to myocardial perfusion defects and an increased rate of cardiac events, CED is considered significant when there is an increase in %ΔCBF ≤50% or a decrease in epicardial coronary artery diameter ≥20% after maximal acetylcholine infusion.[19,20,22] These 2 methods used to identify significant endothelial dysfunction reflect both macrovascular endothelial dysfunction as reflected by the change in epicardial coronary artery diameter and microvascular endothelial dysfunction as reflected by the %ΔCBF that has been determined to be mostly regulated by the resistance of 200 μm or smaller arterioles.[23]

Echocardiography

Echocardiograms were performed by registered diagnostic cardiac sonographers and interpreted by staff echocardiologists who were blinded to coronary endothelial function assessment. Left ventricular ejection fraction was calculated by 2D or M-mode measurements or visually estimated as previously reported on all patients.[6] Significant valvular dysfunction was excluded by 2D and color flow imaging. The left ventricular mass was calculated from M-mode or 2D measurements as previously described[24] and indexed to body surface area. Left ventricular hypertrophy was defined as left ventricular mass indexed to body surface area, 134 and 110 g/m^2 in men and women, respectively.[25,26]

Left ventricular relaxation was evaluated by the tissue Doppler measurement of Ea. Doppler tissue imaging of the velocity of early diastolic ascent of the mitral annulus (Ea) was obtained, from the apical 4-chamber view, using a 1- to 2-mm sample volume placed in the septal mitral valve annulus. This measurement has been shown as a preload-independent measure of the speed of left ventricular relaxation and correlates well with the time constant of left ventricular relaxation measured invasively.[27,28]

Lower Ea values reflect slower myocardial relaxation. Normal Ea values according to age groups have been published.[29] For the purposes of our study, an abnormally low Ea is a value of Ea 1 SD lower than the mean Ea expected for a group of normal subjects within a prespecified age category. For patients younger than 40 years, an abnormally low Ea is an Ea < 0.11 m/s; for patients who are 40 to 60 years old, an abnormally low Ea is an Ea < 0.10 m/s; and for patients older than 60 years, an abnormally low Ea is an Ea < 0.08 m/s.[29]

Statistical analysis

Continuous variables with mildly skewed distributions were summarized as mean ± SD. Those with heavily skewed distributions were summarized as median (first, third quartiles). Discrete variables were presented as frequency (group percentage). For heavily skewed variables (glucose and triglyceride levels), a logarithmic transformation was used in further analysis. Student t test was used to compare continuous variables between groups. χ^2 analysis was used to compare categorical variables between groups. Simple linear regression

Table I. Patient characteristic

	Total population	Normal myocardial relaxation*	Abnormal myocardial relaxation*	P
Number (%)	160	73 (46%)	87 (54%)	
Age (±SD), y	50 ± 12	48 ± 14	51 ± 11	.12
Percent patients age ≥60 y	23	25	21	.55
Women (%)	97 (61%)	46 (63%)	51 (59%)	.57
BMI (±SD), kg/m^2	28 ± 6	27 ± 6	29 ± 6	.056
Percent with BMI 25–30	31	29	32	
Percent with BMI ≥30	36	29	41	
Hypertension (%)	74 (46%)	31 (42%)	43 (49%)	.38
Antihypertensive therapy (%)	54 (34%)	21 (29%)	33 (38%)	.22
Diabetes mellitus (%)	15 (9%)	5 (7%)	10 (11%)	.31
Fasting glucose, median (Q1, Q3), mg/dL	96 (88, 105)	93 (86, 101)	99 (91, 108)	.0055
Current smoker (%)	21 (13%)	11 (15%)	10 (11%)	.74
Previous smoker (%)	65 (41%)	31 (43%)	34 (39%)	.85
Hyperlipidemia (%)	85 (53%)	36 (49%)	49 (56%)	.38
Lipid lowering agent (%)	52 (33%)	20 (27%)	32 (37%)	.21
Total cholesterol (±SD) mg/dL	185 ± 42	175 ± 39	193 ± 42	.0042
Non-HDL cholesterol (±SD), mg/dL	131 ± 41	121 ± 37	139 ± 44	.0048
LDL (±SD), mg/dL	105 ± 32	100 ± 34	109 ± 30	.094
HDL (±SD), mg/dL	54 ± 16	54 ± 17	54 ± 14	.89
Triglycerides, median (Q1, Q3), mg/dL	96 (66, 155)	87 (61, 128)	113 (74, 174)	.0025
No. of patients with mild atherosclerosis† (%)	89 (56%)	37 (51%)	52 (60%)	.25
Hemoglobin level (±SD), g/dL	13.3 ± 1.5	13.1 ± 1.5	13.5 ± 1.5	.22
Creatinine (±SD), mg/dL	1.02 ± 0.02	1.00 ± 0.02	1.04 ± 0.02	.17
C-reactive protein (Q1, Q3), mg/L	4.0 (1.3,7.8)	4.0 (1.1, 8.7)	3.0 (1.3, 7.1)	.90
Coronary flow reserve (±SD)	3.1 ± 0.8	3.2 ± 0.9	3.0 ± 0.8	.23
%ΔCBF (±SD)	53 ± 92	69 ± 102	35 ± 70	.016
Percent change in epicardial coronary diameter to acetylcholine (±SD)	−14 ± 20	−13 ± 19	−19 ± 20	.083
Echocardiographic parameters				
Ejection fraction (±SD)	64 ± 5	64 ± 5	64 ± 5	.44
LVMI (±SD), g/m^2	83 ± 20	81 ± 18	85 ± 21	.28
Percent with left ventricular hypertrophy	6	3	8	.15
E (±SD), m/s	0.77 ± 0.18	0.82 ± 0.20	0.73 ± 0.15	.0004
A (±SD), m/s	0.65 ± 0.19	0.59 ± 0.18	0.69 ± 0.19	.0005
Deceleration time (±SD), ms	205 ± 34	200 ± 33	210 ± 34	.066
Ea (± SD), m/s	0.09 ± 0.03	0.11 ± 0.02	0.07 ± 0.02	<.0001

%ΔCBF, Percent change in CBF to a maximal acetylcholine dose; *LVMI*, left ventricular mass index.
*Myocardial relaxation was considered abnormal if the Ea was 1 SD lower than normal mean for age.
†Mild coronary atherosclerosis was defined as any coronary artery luminal diameter narrowing of 5% to 30%. The rest of the population had normal coronary arteries.

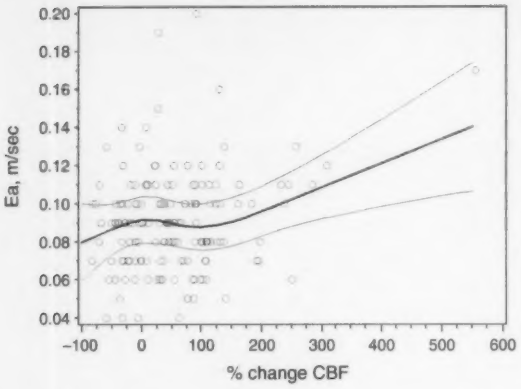
was used to study univariate associations between continuous variables with Pearson correlation coefficients and the *P* value reported. Multiple linear regression was used to investigate whether coronary risk factors influenced diastolic function after adjusting for the presence of CED. All covariates that showed evidence of an association with diastolic function parameters ($P \leq .10$) were included in the multiple linear regression models. Covariates were selected by sequentially removing variables that contributed least to the model. After the covariates were selected, 3 models for the assessment of vascular function (ie, microvascular endothelial function, macrovascular endothelial function, and endothelial independent vascular function [CFR]) were created by adding the variable in the model. That is, each model has the same covariates. Quantile-quantile plots were used to assess the assumption of normally distributed residuals. Restricted cubic splines were used to model nonlinearity between continuous variables and diastolic relaxation.

Results

Patient population

A total of 180 consecutive patients in sinus rhythm, without significant CAD, and who had a normal ejection fraction by echocardiography and no heart failure were eligible for the study. Out these 181 patients, 160 had assessment of diastolic function and accordingly comprised our study population. Echocardiographic evaluation was performed at a median time of 2 days from cardiac catheterization (25th interquartile 1 day; 75th interquartile 6 days). Baseline characteristics of the study population are summarized in Table I (there was a high prevalence of obesity, hypertension, and hyperlipidemia). The mean % change in the coronary artery diameter in response to acetylcholine was −14 ± 20, the %ΔCBF was 53 ± 92, and the

Figure 1



Association of left ventricular relaxation as assessed by Doppler tissue measurement of the velocity of Ea with %ΔCBF in response to acetylcholine (10^{-4} mol/L); $P = .018$.

CFR was 3.1 ± 0.8. By definition, ejection fraction was normal in all patients.

Table I shows the clinical and echocardiographic characteristics of the patient population overall and according to normal and impaired myocardial relaxation. Patients with abnormal myocardial relaxation had higher fasting blood glucose, total cholesterol, non-HDL cholesterol, and triglycerides, and tended to have higher BMI compared to patients with normal myocardial relaxation. Microvascular endothelial function as assessed by %ΔCBF was reduced in patients with abnormal myocardial relaxation as compared to patients with normal myocardial relaxation, whereas no difference was seen in the macrovascular endothelial function and the nonendothelial dependent CFR between the 2 groups.

Univariate associations between left ventricular relaxation (Ea) and patients' characteristics

The speed of left ventricular relaxation (Ea) was directly associated with both the CFR ($r = 0.18$; $P = .03$) and with microvascular endothelial function as assessed by the %ΔCBF ($r = 0.21$; $P < .01$). A trend was seen between a higher Ea and better macrovascular endothelial function as assessed by the mean % change in the coronary artery diameter in response to acetylcholine, ($r = 0.14$; $P = .088$). The speed of left ventricular relaxation was inversely associated with age ($r = -0.52$; $P < .01$); left ventricular mass indexed to body surface area ($r = -0.26$; $P < .01$); BMI ($r = -0.20$; $P = .01$); fasting glucose levels ([log glucose]; $r = -0.23$; $P < .01$); total cholesterol levels ($r = -0.25$; $P < .01$); non-HDL cholesterol levels ($r = -0.23$; $P < .01$); and triglyceride levels ([log triglycerides]; $r = -0.27$; $P < .01$). A lower Ea was seen in hypertensive compared to normotensive patients (0.086 ± 0.028 vs 0.094 ± 0.024 m/s; $P = .04$). A trend for a lower Ea was observed in women compared to men (0.088 ± 0.024 vs 0.094 ± 0.028 m/s; $P = .10$), and in patients with higher LDL values ($r = -0.13$; $P = .10$). No associations between Ea and either HDL ($P = .50$) or smoking status ($P = .90$) were seen.

Table II. Multiple linear regression model for the association between diastolic function as assessed by tissue Doppler diastolic (Ea) and various patient characteristics

	P
Age	<.001
%ΔCBF	.018
Women*	.028
LVMI	.016
Fasting glucose	.080
Non-HDL cholesterol	.022

Results of the multivariate model for the association between diastolic function as assessed by tissue Doppler diastolic (Ea) and various patient characteristics. $r^2 = 0.43$.
*Women vs men.

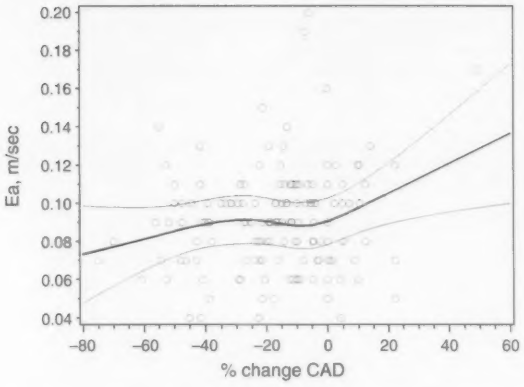
Multivariate associations between left ventricular relaxation (Ea) and patients' characteristics

To gain insight into the association between CED and impaired relaxation, models were created to study the effect of the nonendothelial dependent vasodilatation (as assessed by the CFR) and the endothelium dependent vasodilatation (as assessed by the %ΔCBF and the mean % change in the epicardial coronary artery diameter in response to acetylcholine) after adjusting for coronary atherosclerosis risk factors. Non-HDL cholesterol was used to investigate the role of hyperlipidemia. In the final model, impaired microvascular endothelial dysfunction (Figure 1), older age, female sex, higher left ventricular mass indexed to body surface area, and higher non-HDL cholesterol were independently associated with more impaired relaxation as assessed by tissue Doppler Ea (Table II). The R^2 value was 0.43 for the model, indicating that the model accounted for more than 40% of the variability in Ea measures. Similar results were obtained when non-HDL cholesterol was substituted with total cholesterol or triglycerides (data not shown).

In the multiple linear regression model, macrovascular endothelium dysfunction as assessed by the change in coronary artery diameter in response to acetylcholine showed a significant association with impaired relaxation as assessed by tissue Doppler Ea ($P = .037$) with an $r^2 = 0.43$ for the model (Figure 2).

Nonendothelial dependent microvascular dysfunction as assessed by CFR was not associated with myocardial relaxation as assessed by Ea ($P = .43$).

Figure 2



Association of left ventricular relaxation as assessed by Doppler tissue measurement of the velocity of Ea with % change in epicardial CAD in response to acetylcholine (10^{-4} mol/L); $P = .037$.

Discussion

Summary

In the current study, we observed an association between abnormal coronary endothelial function and the presence of diastolic dysfunction in humans without significant occlusive CAD of heart failure. Specifically, impairment in both microvascular and macrovascular endothelial mediated coronary vasodilation were associated with impairment in left ventricular relaxation. Second, we found that hyperlipidemia was associated with the presence of impaired relaxation even after adjusting for coronary vascular function and other risk factors known to modulate diastolic function.

Relationship between left ventricular relaxation and coronary endothelial function

An association between systolic heart failure and coronary[30] as well as peripheral endothelial dysfunction[31] has been well established. In addition, we have previously shown an association between CED and asymptomatic left ventricular dysfunction.[32] However, no study has evaluated the relationship between coronary endothelial function and a reliable measure of myocardial diastolic function at an asymptomatic stage. The fact that this independent relationship exists very early before the progression of either CAD or diastolic heart failure points out to the possibility of an important pathogenetic role that CED might play in the development of DHF.

A regulatory role of the coronary endothelium on the myocardial performance has been implicated in a study by Paulus et al,[33] where an infusion of intracoronary substance P into normal coronaries of human subjects resulted in increased diastolic distensibility in addition to depressed systolic function. And in experimental models of heart failure with significant diastolic dysfunction, secondary to either left ventricular hypertrophy[8] or type 2 diabetes mellitus,[34] the endothelium-dependent vasodilator pathway has been implicated. Coronary endothelial dysfunction of porcine epicardial coronary arteries in a left ventricular hypertrophy model,[9] of rat models,[7] and of isolated ejecting hearts of aortic-banded guinea pigs[8] has been implicated in impaired myocardial relaxation. All these lines of evidence, in addition to our study, underscore the important role that the coronary endothelium plays potentially in regulating the diastolic function of the heart.

There are multiple of potential mechanisms whereby an impaired endothelial function leads to diastolic dysfunction. Coronary endothelial dysfunction has been associated with myocardial ischemia,[19,35,36] a known factor to lead to impaired relaxation. Alternatively, because of the intricate relation between the large endothelial lining and the myocardium, the endothelium by virtue of its paracrine function has been implicated in myocardial hypertrophy and interstitial fibrosis in a multitude of experimental studies[37] and consequently could lead to diastolic dysfunction.

A recent study by Tschope et al[38] showed a high prevalence of cardiac parvovirus B19 infection in patients with isolated left ventricular diastolic dysfunction. In this study, patients with hypertension, diabetes mellitus, and coronary atherosclerosis have been excluded.[12,38] Nonetheless, when assessed, microvascular CED was observed in the larger proportion of patients with diastolic dysfunction. These observations generate interest in further exploring the hypothesis that CED might be a potential common final pathogenetic mechanism in diastolic dysfunction secondary to a multitude of causes.

Our current observation of an independent associations between coronary atherosclerosis risk factors and diastolic dysfunction at a very early stage is consistent with the epidemiologic study of Fischer et al[12] showing that the prevalence of diastolic abnormalities and diastolic dysfunction is rare in the absence of CAD and its risk factors.

Relationship between left ventricular relaxation and hyperlipidemia

Recently, Fukuta et al[17] showed that statin therapy may be associated with a lower mortality rate in patients with diastolic heart failure. As subsequently discussed by Zile,[39] both lipid-lowering and lipid-independent mechanisms might contribute to the improvement seen with statins in patients with DHF. In experimental animal models, statins have been shown to reduce myocardial hypertrophy and fibrosis.[40,41]

Moreover, we have previously demonstrated that statins improve CED and myocardial perfusion in pigs fed high cholesterol diet without effecting cholesterol levels.[42,43] Interestingly, in our study the association between the lipid level and diastolic relaxation was independent of endothelial function. One can conclude that this association might extend beyond the vasculature and might be having potentially a deleterious effect on myocardial function independent of ischemia. This might be 1 potential mechanism to explain the pleiotropic effects observed with statins beyond their effect on vascular atherosclerosis.

Limitations

This is a retrospective analysis that is subject to the limitations of such analyses, and does not allow us to establish whether CED preceded the onset of the diastolic dysfunction. Nonetheless, the very early observed association of the coronary endothelial function with diastolic function in the absence of CAD and congestive heart failure raises the interest in further exploring the hypothesis that a causative relationship exists between coronary endothelial function and diastolic function. Second, because the study was conducted in patients with chest pain undergoing coronary angiography for evaluation of CAD, selection bias can not be ruled out. However, it would be hard to justify invasive measures of coronary endothelial function in completely asymptomatic patients, and such a study would be unlikely to take place. Third, the noninvasive nature of diastolic assessment might be another limitation, although strong associations with invasive measurements have been established when tissue Doppler assessment has been included.[27,28,44,45] Finally, although known traditional risk factors associated with endothelial and diastolic functions have been analyzed, nontraditional risk factors and genetic predispositions have not been evaluated.

Conclusions

In our study we have observed that an independent association might exist between coronary endothelial function and diastolic function in patients with normal ejection fractions in the absence of significant CAD and heart failure symptoms. We have seen that hyperlipidemia was associated with the presence of impaired relaxation even after adjusting for coronary vascular function and other risk factors known to modulate diastolic function. These data suggest that hyperlipidemia may modulate diastolic function via mechanisms independent of the coronary vasculature.

Finally, our findings underscore the importance of considering future studies to determine if strategies to preserve coronary endothelial function and to lower lipids may improve outcomes in patients with diastolic dysfunction and DHF.

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Impaired peripheral endothelial function in severe idiopathic pulmonary hypertension correlates with the pulmonary vascular response to inhaled iloprost

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Background Pulmonary endothelial function is known to be impaired in subjects with idiopathic pulmonary arterial hypertension (IPAH), but peripheral endothelial dysfunction and its predictive value for pulmonary vasoreactivity have not been previously investigated.

Methods Measurements of peripheral endothelium-dependent and endothelium-independent vasoreactivity using flow-mediated dilation (FMD) and nitroglycerin-mediated dilation of the brachial artery were performed in 18 patients with severe IPAH (15 women; mean age 50 years [95% confidence interval 46-55 years], mean pulmonary artery pressure [PAP] 51 mm Hg [43-59 mm Hg], pulmonary vascular resistance [PVR] 1239 dyn s cm^{-5} [861-1618 dyn s cm^{-5}] at baseline) and in 36 age- and sex-matched controls. In patients with IPAH, acute pulmonary vasoreactivity was measured as pulmonary vascular response to inhaled iloprost (PVRII) during pulmonary catheterization.

Results Compared to controls, patients with IPAH demonstrated impaired peripheral endothelial function (FMD, 0.19 [0.07-0.31] vs 0.38 [0.30-0.44] mm among controls; $P = .002$). No such impairment was observed for nitroglycerin-mediated dilation (0.34 [0.23-0.46] vs 0.36 [0.20-0.51] mm among controls; $P = .679$). Among patients with IPAH, iloprost lowered mean PAP by 8.2 mm Hg (2.0-14.5 mm Hg) ($P = .001$) and PVR by 395 dyn s cm^{-5} (109-680 dyn s cm^{-5}) ($P < .001$). Subsequent analysis of the association between peripheral endothelial function and PVRII disclosed a correlation of FMD with the percent decrease in mean PAP ($r = .65$, $P = .003$) and PVR ($r = 0.67$, $P = .002$), in which patients with IPAH with the greatest PVRII also exhibited the highest FMD values.

Conclusions Idiopathic pulmonary arterial hypertension is associated with peripheral endothelial dysfunction. Peripheral endothelium-dependent vasoreactivity correlates with the PVRII. It remains to be established if FMD has the potential as a clinical tool for noninvasive estimation of pulmonary vasoreactivity in IPAH.

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Where patients with mild to moderate heart failure die: Results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)

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Background Common locations of death in patients with congestive heart failure (CHF) are unknown. In the SCD-HeFT, mortality of patients with CHF was assessed after randomization to an implantable cardioverter/defibrillator (ICD), amiodarone, or placebo. The aim of this study was to evaluate the location of deaths in SCD-HeFT.

Methods Among SCD-HeFT patients whose location of death was identified, we used logistic regression to assess the relationship of randomized treatment arm and other baseline predictors with the location of death. Cause of death was adjudicated by a therapy-blinded events committee.

Results In SCD-HeFT, 666 (26%) of 2521 patients died. Of the 604 (91%) for whom location of death was known, 58% died in hospital and 29% died at home. Patients randomized to receive an ICD were less likely to die at home than patients randomized to placebo ($P = .002$). Fewer patients randomized to ICDs died; even fewer randomized to ICDs died at home. Age, sex, etiology of heart failure, left ventricular ejection fraction, and New York Heart Association functional class were not associated with location of death. Sudden cardiac death represented 52% of all out-of-hospital deaths but in hospital deaths exceeded out-of-hospital deaths.

Conclusion Deaths in SCD-HeFT, a well-treated CHF population, were most often in hospital. ICDs were associated with lower total and sudden death rates at home and in hospital. Development of methods to identify which patients will not respond to optimal treatment, including an ICD, remain a challenge. (Am Heart J 2007;153:1089-94.)

Patients with congestive heart failure (CHF) are at risk of death due to cardiac arrhythmias, worsening heart failure, and noncardiac causes,[1-4] but the location where these patients die is not known. Sudden, unexpected, out-of-hospital, death is considered a common cause of death in the United States[5-7] and likely explains deaths of many patients with heart failure, despite medical therapy. Yet, although many deaths may be out of hospital due to arrhythmic causes, some arrhythmic deaths occur in the hospital. Predictors for in hospital mortality exist based on admission characteristics of hospitalized patients,[8] but no data predict the location of death in an outpatient heart failure population.

One common presumption is that an implantable cardioverter/defibrillator (ICD) or an antiarrhythmic drug may trade a quick and painless death for a lingering, perhaps even miserable, death. Furthermore, ICDs can be associated with limitation in activities including driving. The SCD-HeFT,[9] a large National Institutes of Health–sponsored, multicenter, extended follow-up clinical trial evaluated the mortality of patients with chronic CHF (New York Heart Association [NYHA] functional class II and III), who had left ventricular ejection fractions ≤0.35 and were treated with standard heart failure medications. Patients were randomized as outpatients to receive a single-lead ICD, amiodarone, or a placebo pill (double blind with amiodarone). SCD-HeFT offered the opportunity to assess the impact of adjunctive arrhythmia treatment strategies (vs placebo) on the location and mode of death in this ambulatory chronic heart failure population.

The purpose of this study was to examine the place of death (in hospital, at home, or elsewhere) in SCD-HeFT. We hypothesized that most deaths in SCD-HeFT occurred in the hospital but that the location of death could not be predicted reliably by clinically available parameters.

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We further hypothesized that at-home deaths were even less frequent in patients randomized to receive an ICD.

Methods

SCD-HeFT Background

In SCD-HeFT, 2521 patients with NYHA functional class II and III heart failure were randomized in equal proportions to placebo pills, amiodarone pills (double blinded), or single-chamber, shock-only ICDs that were primarily implanted in an outpatient setting.

Patients were expected to be treated optimally with medical therapy for NYHA functional class II and III heart failure unless clinically unreasonable. In SCD-HeFT, 69%/78% (at trial onset/at last visit, respectively) of patients received a β-blocker, 85%/72% received an angiotensin-converting enzyme inhibitor, 96%/87% received an angiotensin-converting enzyme inhibitor and/or an angiotensin receptor blocker, 82%/80% received a loop diuretic, and 19%/31% received an aldosterone blocker consistent with well-managed medical therapy. The median patient follow-up period was 45.5 months.

Data Evaluation

Patients enrolled in SCD-HeFT who died during the trial and whose location of death was known were included in this analysis (n = 604). All deaths were assessed and adjudicated by an events committee systematically blinded to the test therapy. Deaths were identified as sudden, cardiac, arrhythmic, or due to progressive heart failure by using preselected definitions.[10] Data on patient deaths were reviewed and classified by the clinical events committee as sudden cardiac death if death was deemed cardiac, arrhythmic, and sudden. Deaths were categorized as occurring in the hospital, at home, at an extended-care facility, or at other locations. Location of death was determined by patient records and information from treating physicians and family members.

Statistics

Descriptive summaries of location of death are given in terms of frequencies and percentages. The randomized treatment arms were compared with respect to location of death by using the conventional χ^2 test. The relationship of modes of death to location of death was similarly assessed by χ^2 tests. Logistic multiple regression was used to assess the relationship of randomized treatment arm and other baseline predictors with whether or not death occurred at home. Baseline predictors considered were age, sex, left ventricular ejection fraction, NYHA functional class, and heart failure etiology (ischemic vs nonischemic). Whether a patient was living alone at the last visit before death was also considered as a predictive factor. The logistic model was also used to formally test whether differences in location of death among treatment arms varied across subgroups defined by NYHA class and CHF etiology, that is, to assess interactions between treatment and NYHA functional class and between treatment and heart failure etiology (each interaction tested with 2 *df*). Within these subgroups, relative risks between treatment arms for dying at home were generated from the logistic model. In addition to the variables listed above, the number of hospitalizations per year for each patient (excluding the final hospitalization for those who died in hospital) was examined with the logistic model to evaluate its relationship to location of death. We further examined whether the frequency of hospitalizations reflected a different association with location of death in the 3 treatment arms (ie, whether an interaction existed between hospitalization frequency and treatment. For all analyses, $P \leq .05$ was considered statistically significant. No adjustments were made for multiple comparisons.

Table I. Location of death by randomization arm

Location	All patients (n = 604)	ICD (n = 170)	Placebo (n = 218)	Amiodarone (n = 216)
In hospital	352 (58)	107 (63)	112 (51)	133 (62)
At home	178 (29)	37 (22)	79 (36)	62 (29)
Extended-care facility	42 (7)	16 (9)	19 (9)	7 (3)
Elsewhere	32 (5)	10 (6)	8 (4)	14 (6)

Values are presented as number (%). $P = .004$ for overall 4×3 χ^2 test of any difference in location of death by randomization arm. The difference in the proportion of at-home deaths between ICD and placebo arms is highly significant ($P = .002$).

Table II. Location of death—by clinical characteristic

	In hospital	At home	Elsewhere	P*
Age	65 (58, 71)	64 (56, 70)	67 (56, 74)	.21
Women	20 (72)	15 (27)	16 (12)	.20
Ischemic†	65 (228)	67 (119)	69 (51)	.90
EF	22 (19, 28)	23 (20, 28)	22 (17, 28)	.54
NYHA III	48 (168)	45 (80)	36 (27)	.93
Living alone	20 (68)	24 (43)	24 (18)	.23

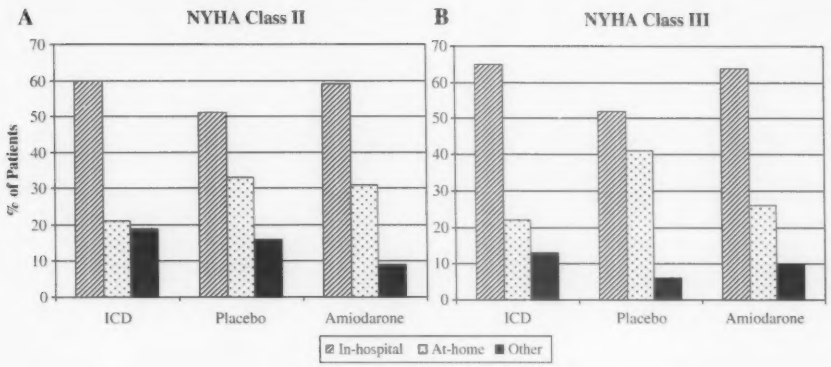
Age and EF are expressed as median (25th, 75th percentiles); other variables, as percent (patient number). *EF*, Left ventricular ejection fraction.
*From logistic regression model for likelihood of dying at home, containing all characteristics in the table plus randomized treatment arm.
†Ischemic etiology of the heart failure.

Results

In SCD-HeFT, 2521 patients were enrolled (847 in the placebo, 845 in the amiodarone, and 829 in the ICD arms). The median age was 60.1 years, 23% were women, and 23% were minorities. Other patient characteristics have been reported previously.[9]

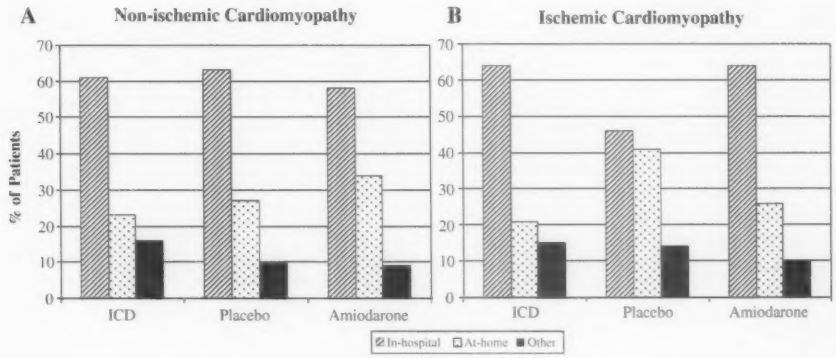
A total of 666 (26%) patients died during the study. The location of death was known in 604 (91%) of these patients but was not available for 62 patients who died (12 ICD, 26 placebo, 24 amiodarone). Among the 604 deaths where location was known, most occurred in the hospital or at home: 58.3% in the hospital, 29.5% at home, and 6.9% at an extended-care facility, accounting for 94.7% (Table I). The remaining 5.3% died elsewhere. Eighteen died away from home: in an airport, hotel room, cruise ship, public place, camping or "in the woods" (n = 8), in a vehicle (n = 5), in the emergency department (n = 3), "in hospital parking lot—leaving" (n = 1), or at work (n = 1). Fourteen died en route to the hospital.

Figure 1



Percent of deaths by location, randomized therapy, and NYHA functional class. A, Location of death by randomized therapy NYHA class II. B, Location of death by randomized therapy NYHA class III.

Figure 2



Percent of deaths by location, randomized therapy, and etiology of heart failure. A, Location of death by randomized therapy in non-ischemic cardiomyopathy. B, Location of death by randomized therapy in ischemic cardiomyopathy.

The median time from randomization to death for those with in hospital deaths was 22 months, for those who died at home was 20 months, and for those who died elsewhere was 25 months. In logistic multiple regression analysis of baseline clinical characteristics with whether death occurred at home, there were no significant associations between patient characteristics and location of death (Table II) (all $P > .2$).

Location of death by trial arm

The number of deaths was lowest in the ICD arm (as reported previously[9]). Most deaths in each treatment arm occurred in the hospital (Table I). The numbers of in hospital deaths in the ICD and placebo arms were similar (107 and 112, respectively), with a larger number (n = 133) in the amiodarone arm. The major difference among the treatments was in the number of deaths occurring at home (37 in the ICD arm vs 79 and 62, respectively, in the placebo and amiodarone arms (Table I). The overall comparison of the 3 treatment arms by the 4 locations of death (Table I) was statistically significant ($P = .004$).

Location of death by treatment in NYHA class and heart disease subgroups

Location of death information for patient subgroups defined by NYHA class (class II/III) (Figure 1, *A* and *B*) and by CHF etiology (ischemic/nonischemic) (Figure 2,

Table III. Location of death by treatment for subgroups defined by heart disease type and NYHA class

	Odds ratio (95% CI) for dying at home*	
Subgroup	**Placebo vs ICD**	**Placebo vs amiodarone**
Ischemic	2.78 (1.57-4.92)	2.03 (1.22-3.38)
Nonischemic	1.20 (0.53-2.73)	0.71 (0.35-1.44)
NYHA class II	1.87 (0.97-3.62)	1.10 (0.65-1.86)
NYHA class III	2.59 (1.34-5.00)	2.05 (1.09-3.86)

*From logistic regression subgroup models among patients who died.

Table IV. Cause of death by location: at home versus in hospital

Cause of death	In hospital	At home	Elsewhere
Sudden cardiac death	18 (63)	58 (103)	38 (28)
Nonsudden cardiac death	52 (184)	25 (44)	31 (23)
Noncardiac death	29 (103)	16 (29)	30 (22)
Unknown	1 (2)	1 (2)	1 (1)

Values are expressed as percent (number of deaths). $P = .001$ for overall test of any difference in mode of death by location of death.

A and *B*) reflects a consistently higher percentage of deaths in hospital for all treatment groups. The test for an interaction between treatment arm and NYHA functional class was not significant ($P = .31$). Similarly, the test for an interaction between treatment arm and heart failure etiology was not significant ($P = .071$). In the ischemic cardiomyopathy and NYHA functional class III subgroups, death was more likely to occur at home for the placebo patients than for the ICD or amiodarone patients (odds ratio >2 for all comparisons of placebo to others) (Table III).

Categorization of death by location

Cause of death was assessed by location (Table IV). Seventy-three percent of the nonsudden cardiac deaths occurred in the hospital, but nonsudden cardiac deaths constituted 52% and 25% of the in hospital and at-home deaths, respectively. Sudden cardiac deaths occurred more often out of the hospital and were generally at home, yet 32% of the sudden cardiac deaths were in the hospital. Fifty-two percent of deaths occurring out of the hospital were sudden cardiac deaths.

Whereas 52% of in hospital deaths were nonsudden cardiac deaths, 18% of in hospital deaths were sudden cardiac deaths, and 19%[12] of the total in hospital sudden cardiac deaths occurred in the ICD arm. Of the in hospital deaths, 29% were noncardiac. The overall comparison of the 3 locations of death by 4 modes of death (Table IV) was statistically significant ($P = .001$).

Hospitalizations and death—is there a relationship?

Hospitalizations were common in SCD-HeFT; 66% of the total population was hospitalized at least once. Eighty-three percent (504) of patients whose death location was known had been hospitalized before death. Among 352 who had an in hospital death, 178 patients who died at home, and 74 patients who died elsewhere, 321 (91%), 122 (69%), and 61 (82%), respectively, had a prior hospitalization. Hospitalizations per year was not a significant predictor of dying at home ($P = .66$; OR, 1.02; 95% CI, 0.95-1.09). There was no significant interaction between randomized therapy and hospitalizations per year ($P = .52$), indicating that this lack of association between hospitalization and location of death was consistent across treatment arms.

Of those hospitalized before they died, 75% were hospitalized <2 months before death. Of 265 hospitalization records that had adequate data recorded, the median (25th, 75th percentiles) length of stay was 7 days[4,14] in the final hospitalization before death. In the 2 weeks before death, 51% who died at home and 26% who died in the hospital had progressive heart failure recorded. In the 2 weeks before death, 14% who died at home and 4% who died in hospital had evidence of progressive ischemic disease recorded.

Discussion

SCD-HeFT included a large population of ambulatory patients with NYHA functional class II and III heart failure treated with standard medical therapies. Among the SCD-HeFT patients who died, the most common location of death was in the hospital. The second most common location was at home. These results may appear surprising. Out-of-hospital death due to ventricular fibrillation is considered a common cause of death in the general population,[6,7] but the risk of out-of-hospital death may be overestimated especially in the heart failure population. The location and risk of heart failure–related death could be changing with improved medical management and with ICDs.

Our understanding regarding location and cause of unmonitored out-of-hospital death may be rudimentary. Retrospective, death certificate–based surveillance overestimates the sudden cardiac death incidence. Sudden cardiac deaths may be less common than suspected.[11] Assumptions that most out-of-hospital sudden deaths are cardiac may be incorrect.[12,13]

The ESVEM study, performed before routine use of ICDs or β-blocker therapy, showed that in hospital death was common in patients with structural heart disease at risk for ventricular arrhythmias. The risk of out-of-hospital arrhythmic death was higher in ESVEM than in SCD-HeFT, but therapies and patient populations differed.[14]

In hospital location of death may depend, in part, on perceived benefits and needs of hospitalization. In hospital death rates in patients with coronary heart disease may be declining at a greater rate than out-of-hospital deaths.[15] From 1979 to 1998, annual coronary heart disease death rates declined 5.3% for in hospital deaths versus 1.8% for out-of-hospital deaths.[16] Canadian in hospital death rates peaked in 1994 at 80.5% and declined subsequently.[17]

When questioned, patients near end of life value interpersonal relationships, functionality, fewer symptoms, and reduced pain.[18] Hospitalization may not offer these opportunities. In one report of elderly and seriously ill patients who ultimately died, 63% had difficulty tolerating physical and emotional symptoms before death. Most (59%) preferred treatment that focused on comfort, as pain and other symptoms were commonplace and troubling. Still, 11% had a final resuscitation attempt.[19]

It is difficult to determine which heart failure patient will die in the hospital, who benefits the most from hospitalization, how to council patients about hospitalization, and how to judge location of death.[20,21] Sudden death (by definition, unexpected) is different than dying at home surrounded by family who expect death is imminent. In the SCD-HeFT population, 58% of the at-home deaths were sudden.

In SCD-HeFT, sudden cardiac deaths occurred in hospital even with ICD implants. Although a lower total number of out-of-hospital deaths in the ICD arm of SCD-HeFT could be explained readily, the lack of effect of the ICD to prevent in hospital sudden deaths was not understood. Perhaps, such patients could not have been resuscitated by any means, because death, sudden or not, may have been inevitable.[22,23] Similarly, in one report of ICD recipients, 64% of out-of-hospital sudden deaths in such patients were tachyarrhythmia associated.[3] Sudden death may also be due to noncardiac causes such as a pulmonary embolus or a ruptured aorta.

ICD programming in SCD-HeFT minimized pacing intentionally. It was unlikely, therefore, that the ICD exacerbated heart failure and hospitalizations by virtue of pacing. However, despite the high trigger rate for shock intervention, inappropriate shocks might have exacerbated heart failure occasionally.[24]

Other findings deserve attention. The placebo arm of the ischemic cardiomyopathy group had a higher incidence of at-home deaths but the cause for this was not known. In hospital death rates were greater in the amiodarone arm compared with other treatment arms but the cause for this was also unknown. The apparent increase in mortality for NYHA class III patients treated with amiodarone, compared to placebo, supports this thesis.[12]

The findings from this study may underscore the need to consider ICD deactivation in end-stage patients. A retrospective cohort telephone survey regarding ICD deactivation in patients near end of life indicated that ICD deactivation was discussed rarely (27 of 100 cases) and generally too late.[25] The results of our study do not provide insight into the important yet generally unexplored area of quality of death in patients with ICDs.

This report underscores the need to better understand how to properly select patients who may benefit from an ICD. It appears that some patients are too healthy and are at too low a risk, and others are too sick. Those who are too sick may have some benefit from an ICD but die anyway. Better understanding of the actual additional benefit of an ICD is needed in a heart failure population regarding overall survival in lieu of adverse events and unnecessary shocks that will not necessarily fend off an inevitable, natural death.[26]

Limitations

As is true in other large clinical trials, it was not possible to determine with certainty the cause of all deaths in SCD-HeFT.[27-29] A ventricular arrhythmia may be a manifestation of a dying heart rather than a treatable cause of death, but the adjudication of the relationship of an arrhythmia and death may be biased by the location of death. The level of certainty in assigning a cause for death was related to the rigor with which the event committee adjudicated outcomes.[10]

Findings in the ICD arm of SCD-HeFT apply solely to single-lead ICDs programmed conservatively. The mechanism and location of death may differ for patients receiving dual-chamber ICDs, resynchronization therapy ICDs, or single-lead ICDs programmed more aggressively.

Conclusions

The most frequent location of death in SCD-HeFT, a large population of ambulatory heart failure patients, was in the hospital. Home was the second most likely place to die. Location of death could not be predicted by clinically available parameters. Single-lead ICDs, programmed conservatively, reduced the risk of death. Those patients not receiving ICDs died more commonly out of hospital, generally at home, and of sudden death. Development of methods to identify which heart failure patient will not respond to optimal treatment and will die in the hospital remain a challenge.

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